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AN ANTI-DIABETOGENIC EFFECT OF A PRIMARY ALCOHOLIC EXTRACT OF PITUITARY TISSUE ADMINISTERED ORALLY*

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IN view of the well established fact that the adrenal glands play a certain, though as yet none too well defined, rôle in carbohydrate metabolism, and since a medullotrophic effect has been obtained following the oral administration of a primary alcoholic extract of prime pituitary tissue,¹ it seemed advisable to determine the effect of this same extract administered orally on diabetic patients as well as on laboratory animals, both normal and depancreatized. The results that have been obtained in the early stages of this investigation have been so encouraging that this preliminary report of them is being made.

The results which are reported here have been obtained in experiments carried out for the specific purpose of obtaining leads. No experiment is in any sense a comprehensive one, but, as will be seen, the lead which it was hoped might emerge from these first "spotting" experiments has materialized, and now it will be possible to plan and carry out experiments both on diabetic patients and on animals to determine the full significance of the observations already made.

EXPERIMENTS ON DIABETIC SUBJECTS

CASE 1

A severe case of diabetes in a male, aged 35 years (disease of 16 years' duration), on a fixed regimen of diet (F. 50, P. 70, C. 250) and insulin (40-0-40), employed as a technician in this laboratory. The man was practically sugar-free during the day, but passed considerable sugar during the night and prior to his morning dose of 40 units of insulin. The night urine for four days prior to the experiment was 1,700 c.c.—32 g. sugar; 1,400 c.c.—24 g. sugar; 1,500 c.c.—25 g. sugar; 1,450 c.c.—91 g. sugar. He was then given 6 c.c. of the pituitary extract (1=½) t.i.d. before meals. The first

night urine specimen after this was 950 c.c.—40 g. sugar; the second was 950 c.c.—12 g. sugar; the third 700 c.c.—5 g. sugar. The morning dose of insulin was reduced to 30 units. At 4 p.m. on this, the 4th, day he felt that an insulin reaction was imminent, a blood sugar was taken immediately and it was 53 mg. per cent. He was given a chocolate bar, and later he ate his regular evening meal, but no insulin was given. The next night's specimen was 2,500 c.c.—147 g. sugar. The next day he took 20 units of insulin before breakfast and 30 before dinner. The urine for the following night was 500 c.c.—5 g. sugar. The next day his insulin dosage was 30-0-30. As he was practically sugar-free at 10 p.m. he was given a glass of milk and a biscuit to ensure a safe night. The urine volume for that night was 850 c.c.—25 g. sugar. The next day insulin, 30-0-30, was given, but only one dose of extract, and that before breakfast. The night specimen following this was 1,500 c.c.—68 g. sugar. The following day insulin 30-0-40 and 6 c.c. of extract before breakfast were given: urine, 900 c.c.—24 g. sugar; next day, insulin (40-0-40) but no extract: urine 800 c.c.—7 g. sugar; next day, insulin (40-0-40), no extract: urine 1,375 c.c.—40 g. sugar.

CASE 2

The morning A.C. blood sugar of a mildly diabetic man of 71 years of age, not on insulin, was 250 mg. per cent. He was given 2 c.c. of the pituitary extract (1=1) daily before breakfast for 14 days, and subsequently 3 c.c. b.i.d. for 3 weeks, then 3 c.c. once daily for 1 week. His morning A.C. blood sugar was 180 after 14 days, 153 after 24 days, 135 after 36 days, and 173 after 43 days.

CASE 3

A female, coloured, aged 37, not on any special treatment. A.C. blood sugar, 293. She was given 3 c.c. extract (1=½) t.i.d. for 3 days: A.C. sugar 202.

CASE 4

A male, aged 66, not on insulin. A.C. blood sugar, 198. He was given 3 c.c. extract b.i.d. for 2 days, t.i.d. one day. A.C. sugar 211.

CASE 5

Female, age 53, new admission, no treatment. A.C. sugar 295. Given 3 c.c. extract b.i.d. for 3 days. A.C. sugar, 344.

EXPERIMENTS ON SUBJECTS WITH NORMAL BLOOD SUGAR

1. A male, 52 years of age. A.C. blood sugar 100. Given extract, 3 c.c. t.i.d. for 3 days. A.C. sugar 100.

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2. A female, 38 years of age. A.C. blood sugar 96. Given extract, 3 c.c. t.i.d. for 3 days. A.C. blood sugar 104.

3. A male, 35 years of age. A.C. sugar 104. Given extract, 3 c.c. t.i.d. for 3 days. A.C. sugar 83.

4. A female, 37 years of age. A.C. 130. Given extract 3 c.c. t.i.d. for 4 days. A.C. 100.

EXPERIMENTS ON MONKEYS (MACACA MULATTA)

Normal monkeys.—After an 18 hours' fast a monkey was injected subcutaneously with 5 c.c. of the special extract designed for oral administration ($1=1\frac{1}{2}$). The following blood sugar values were obtained: Control 100; $\frac{1}{2}$ hour 100; $1\frac{1}{2}$ hrs. 83; 2 hrs. 71; 3 hrs. 67; 5 hrs. 92. This same monkey, after an 18 hours' fast, a few days later was given 75 c.c. of a similar extract ($1=1\frac{1}{2}$) by stomach tube. The blood sugar curve was: Control 79; 1 hr. 71; 2 hrs. 79; $2\frac{1}{2}$ hrs. 75; 3 hrs. 58; $3\frac{1}{2}$ hrs. 83; 4 hrs. 71; 5 hrs. 63; 21 hrs. 104.

Another monkey treated likewise first by injection (5 c.c.) and later by stomach tube (75 c.c.) gave the following blood sugar values. (1) After injection: Control 100; $\frac{1}{2}$ hr. 132; 1 hr. 104; $1\frac{1}{2}$ hrs. 111; 2 hrs. 107; 3 hrs. 75; 5 hrs. 111. (2) After stomach-tube feeding: Control 120; 1 hr. 74; 2 hrs. 54; $2\frac{1}{2}$ hrs. 88; 3 hrs. 75; $3\frac{1}{2}$ hrs. 74; 4 hrs. 96; 5 hrs. 58; 21 hrs. 58.

Four monkeys were given 50 c.c. of extract by stomach tube after an 18 hours' fast, and the following blood sugar values were noted. (1) Control, 115; $2\frac{1}{2}$ hrs. 100; 3 hrs. 88; $3\frac{1}{2}$ hrs. 96; 4 hrs. 96; 5 hrs. 137; 22 hrs. 88. (2) Control, 88; $2\frac{1}{2}$ hrs. 71; 3 hrs. 75; $3\frac{1}{2}$ hrs. 111; 4 hrs. 115; 5 hrs. 92; 22 hrs. 79. (3) Control, 115; $2\frac{1}{2}$ hrs. 88; 3 hrs. 100; $3\frac{1}{2}$ hrs. 96; 4 hrs. 120; 5 hrs. 111; 22 hrs. 100. (4) Control, 75; $2\frac{1}{2}$ hrs. 54; 3 hrs. 67; $3\frac{1}{2}$ hrs. 79; 4 hrs. 92; 22 hrs. 92. Food was given in all cases after the 5 hr. blood sample had been taken.

A monkey which was depancreatized 7 months previously had been maintained on a constant diet and 3 units of insulin daily. This animal showed no appreciable change in sugar excretion over a period of 9 days during which 5 c.c. of extract was injected twice daily. A blood sugar curve was taken on this animal at the beginning of this experiment, following a single subcutaneous injection of 5 c.c. of the extract after an 18 hours' fast; it was: Control

288; $\frac{1}{2}$ hr. 280; 1 hr. 317; $1\frac{1}{2}$ hr. 330; 2 hrs. 289; 3 hrs. 220; 5 hrs. 210.

EXPERIMENTS ON RABBITS

Seven out of 10 rabbits fasted 20 hours and given 40 c.c. of the extract by stomach tube showed the following decreases in blood sugar respectively: 42, 16, 13, 32, 17, 19 and 13 mg. per cent after 3 hours.

EXPERIMENTS ON RATS

No appreciable difference has been seen in the degree of hypoglycæmia following fasting in rats treated by stomach tube with 5 c.c. of extract and the untreated controls. Average blood sugar of 10 animals after 16 hours fast was 88; average blood sugar of 8 controls was 87.

RESPIRATORY QUOTIENT

During the past three years, in connection with the studies that have been made in this department on the specific metabolic principle of pituitary extracts, several hundred estimations of the effect on the rate of oxygen consumption of various extracts upon rabbits have been made. The open Haldane method has been used, and this has allowed of the determination of the respiratory quotients. While the usual effect of potent extracts of the metabolic principle is a lowering of the respiratory quotient associated with an increased rate of oxygen consumption, it has been noted that certain extracts have tended to cause the R.Q. to rise during the first two hours of the experiment. Since this is a time when excitement of the animal is most likely to occur, we have tended to disregard this effect on the R.Q. This was probably a mistake in judgment since it is found now that the alcohol-free extracts prepared from the primary alcoholic extract when administered to rabbits by injection tend to raise the R.Q. In 40 experiments, in 7 of which this extract and in 33 of which other types of extract were used, an increase in the R.Q. was noted in the first two hours following the injection of the extract of from 0.03 to 0.21. In two experiments on monkeys, fasted overnight and injected subcutaneously with 5 c.c. of extract ($1=1\frac{1}{2}$), the R.Q. rose in the first two hours from 0.75 to 0.79 and 0.77 to 0.81 respectively.

ASSOCIATED PROPERTIES OF THE PRIMARY ALCOHOLIC EXTRACT OF WHOLE PITUITARY GLAND

In addition to the medullotrophic effect of this extract which has been obtained after either

feeding or parenteral administration, assays have been made for other pituitary principles. Oral administration results in no appreciable change in the metabolic rate. A small amount of specific metabolic factor is present, however, and has been demonstrated following administration by injection to rabbits. The extract contains the glycotropic principle, but this is not effective in increasing glycogen stores unless given by injection to the test animal, the mouse. The extract is rich in the melanophore principle. It contains as well some corticotrophic substance. The only effects which have been obtained consistently following oral administration are the medullary reaction in the adrenal gland of the hypophysectomized rat and the mild hypoglycæmic reactions seen in normal fasted monkeys and rabbits. The latter effect, while fairly consistent, has not been remarkably striking, and indeed might be disregarded by some familiar with the possible vagaries of blood sugar curves. I have found in protocols of experiments carried out in this laboratory in 1935 and 1936 examples of the hypoglycæmic action of certain extracts which are in some instances even more striking than these reported now. At that time the results were discounted because of the large volume of extract which had to be injected to produce the effect, but more particularly because it was shown that a dilute solution of alcohol (13 to 19 per cent) injected intravenously might cause a marked fall in blood sugar level. Blatherwick *et al.*,² it may be recalled, showed that alcohol by the oral route lowered the blood sugar of rabbits. Alcohol has been removed from the extracts used on animals in tests for the effects on blood sugar. I feel that the evidence obtained in the rather simple experiment carried out in case 1 shows that the oral administration of the special extract has influenced profoundly the ability of this individual to handle carbohydrate. This is, I think, the most positive finding that I have to report at this time, and I am of the opinion that the results obtained in the animal experiments are contributing evidence to the significance of this result.

The single experiment on the depancreatized monkey suggests that the extract has no effect in the absence of the pancreas. It is possible, therefore, that the character of the response of different diabetic subjects to this type of treatment may indicate whether or not the diabetes

in the individual case is due to primary pancreatic failure or to an extra-pancreatic factor. Cases responding to extract might be assumed on this reasoning to have a fairly normal pancreas.

Although this work is as yet in an early stage of development a number of interesting questions arise from it, the answers to which cannot be given until much more work has been done. Some of these are.

1. What is the mechanism by which some constituent (or constituents) of the primary alcoholic extract of whole pituitary tissue administered orally affects carbohydrate metabolism?

2. Is the effect upon carbohydrate metabolism produced by the same substance which causes the medullary reaction in the adrenal of the hypophysectomized rat?

3. If so, is the effect upon carbohydrate metabolism secondary to some form of activation of the adrenal medulla, or is it due to a direct action of the substance in the periphery?

4. Is there a true pancreatotrophic hormone as has been claimed,^{4, 13} and, if so, is the effect upon carbohydrate metabolism of this extract due to direct activation of the islet tissue?

5. Is there some type of synergistic action between some constituent of this extract and insulin?

6. Is the medullary reaction secondary to a primary pancreatotrophic action?

7. What is the relationship of the substance affecting carbohydrate metabolism to the diabetogenic substance effective by injection of crude extracts containing it?

The answers to these and many other questions must wait solution, and it may be hoped when this has occurred that the whole problem of carbohydrate metabolism and of diabetes may be seen in a clearer light.

REVIEW OF EARLIER WORK

In order that the results of the experiments included in this paper may be considered in the light of earlier work on the subject, the following review of the more important literature is given.

Horsters³ described the production of hypoglycæmia in fasting rabbits treated by injection with 50 guinea-pig units of the Junkman-Schoeller preparation of the thyrotrophic hormone. In patients with hepatic insufficiency or

diabetes (mild) doses of 500 units had the same effect. Healthy persons showed relatively little effect. Urine volume was increased and there was retention of phosphate. The diabetics seemed to show improved sugar tolerance. Chlorides rose and uric acid fell in the blood.

Shortly after this paper appeared an attempt was made in this laboratory to confirm the claim that the thyrotrophic hormone extract produced hypoglycæmia. We were unsuccessful in this, using our own preparation of thyrotrophic hormone.

Anselmino, Herold and Hoffmann⁴ claimed that the injection of a crude extract made from acetone dehydrated and defatted anterior lobes into young intact rats produced in a few days a marked increase in the number and size of the islets of Langerhans. They ascribed this increase to the action of a pancreatotrophic substance believed to be present in the pituitary gland. It was claimed also to stimulate the secretion of insulin as shown by the fall of blood sugar occurring immediately after injection (Hoffmann and Anselmino⁵). Additional papers were published on the same subject by Anselmino *et al.*,⁶ Leyton and Jones,⁷ and Elmer *et al.*,⁸ failed to confirm their work, while Chrzanowski and Grzycki⁹ did confirm it. These latter authors claimed that a pH 5.2 ultra-filtrate of an aqueous extract of acetone-dried pituitary gland can stimulate formation of islet tissue, while crude aqueous extracts were inactive. Islet hypertrophy after the administration of crude pituitary extract has been reported by Aron¹⁰ and Bierring,¹¹ while Florentin and Picard¹² found that injections of thyroxin, œstrin, posterior pituitary extract and insulin may all cause an increase in the size and number of islets. More recently Richardson and Young¹³ have made a very critical study of the so-called pancreatotrophic action of anterior pituitary extracts. They summarized the results of their extensive and carefully controlled investigations as follows.

"1. A quantitative method of evaluating the ratio islet tissue/acinar tissue for the pancreas of the rat has been applied to the question of the 'pancreotropic' (Anselmino and Hoffmann) action of an extract of ox anterior pituitary gland.

"2. The mean value of this ratio for a group of eleven Wistar-strain white rats injected daily for 2 to 3 weeks with a saline extract of

fresh gland was double that for ten control animals: the difference between these mean values is shown to be statistically significant. As the total amount of acinar tissue was increased rather than decreased, the increase in the ratio islet tissue/acinar tissue must indicate an increase in the absolute amount of islet tissue.

"3. The results of Anselmino *et al.* were not confirmed, in that a significant increase in the mean value of the islet/acinar ratio was not found for a group of ten rats receiving an aqueous extract of acetone-desiccated gland.

"4. In numerous instances the pancreases of experimental animals exhibited giant islets and a histological picture which has been interpreted by many investigators as indicative of proliferative activity of islet tissue. Since, however, such an appearance was frequently not accompanied by an increase in the islet/acinar ratio, it cannot be cited as satisfactory evidence of a significant increase in the amount of islet tissue.

"5. While the increase observed in the Wistar-strain rats we have used appears to be statistically significant, the fact that normal rats of the only other strain examined showed a widely different islet/acinar ratio suggests the necessity of caution in drawing any general conclusion.

"6. The extract which increased the islet/acinar ratio of the pancreas had little or no effect on the blood-sugar level of our rats. The significance of this result is discussed."

COMMENTS

It appears to the writer, in the light of the work past and present on this subject, that it would be fair to conclude that anyone who has worked with either primary alcoholic or aqueous pituitary extracts of prime tissue has had in them an active principle capable of producing a degree of hypoglycæmia. It is of interest in this connection that whereas Richardson and Young, while failing to confirm Anselmino *et al.* on the pancreatotrophic effect of aqueous extracts of acetone dried material such as the latter investigators used, did obtain results which were statistically significant when saline extracts of fresh tissue were used. With regard to the hypoglycæmic effect of anterior lobe extracts, Richardson and Young state: "There is no evidence that the slight hypoglycæmic action of crude pituitary

extract, observed by us and other investigators, is of physiological significance and is due to stimulation of insulin secretion by the pancreas; until further evidence has been obtained it would seem wise to suspend judgment. It should be pointed out that there is as yet no evidence that any islet tissue formed under the influence of pituitary extracts is capable of secreting insulin."

SUMMARY

The results of a preliminary study of the effects of the oral administration of a pituitary extract prepared from the primary alcoholic extract of prime whole gland tissue upon diabetic patients and upon normal rabbits, rats and monkeys, and one depancreatized monkey are reported. Evidence that the extract has a profound effect upon carbohydrate metabolism has been obtained, but the significance of this is yet to be determined.

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ments on most of the human subjects, and to thank him most heartily for this. The technical assistance of Mr. A. A. Long, Mr. G. S. Stewart, B.Sc., Mrs. H. Seoggan, M.Sc., Mrs. K. Nielsen, Mr. E. Pedersen, Mr. E. A. Andersen and Mr. D. McKinnon is gratefully acknowledged.

REFERENCES

1. COLLIP, J. B.: *Canad. M. Ass. J.*, 1940, 42: 2.
2. BLATHERWICK, N. R., MAXWELL, L. C. AND LONG, M. L.: *Am. J. Physiol.*, 1924, 67: 346.
3. HORSTERS, H.: *Arch. exp. Path. Pharmac.*, 1933, 169: 537.
4. ANSELMINO, K. J., HEROLD, L. AND HOFFMANN, F.: *Klin. Wchnschr.*, 1933, 12: 1245.
5. HOFFMANN, F. AND ANSELMINO, K. J.: *Klin. Wchnschr.*, 1933, 12: 1436.
6. ANSELMINO, K. J., HEROLD, L. AND HOFFMANN, F.: *Zeitschr. f. ges. exp. Med.*, 1935, 97: 329.
- ANSELMINO, K. J. AND HOFFMANN, F.: *Klin. Wchnschr.*, 1933, 12: 1435.
- ANSELMINO, K. J. AND HOFFMANN, F.: *Arch. exp. Path. Pharmac.*, 1936, 181: 674.
- ANSELMINO, K. J. AND HOFFMANN, J.: *Klin. Wchnschr.*, 1936, 14: 999.
7. LEYTON, O. AND JONES, R.: *Proc. Roy. Soc. Med.*, 1936, 29: 736.
8. ELMER, A. W., GIEDOSZ, B. AND SCHEPS, M.: *Comptes rendus, Soc. Biol., Paris*, 1937, 124: 823.
9. CHRZANOWSKI, B. AND GRZYCKI, S. J.: *Klin. Wchnschr.*, 1937, 16: 488.
10. ARON, M.: *Comptes rendus, Soc. Biol., Paris*, 1933, 113: 1071.
11. BIERRING, K.: *Bull. Hist. Appl.*, 1934, 11: 297.
12. FLORENTIN, P. AND PICARD, D.: *Rev. franç. Endocrin.*, 1936, 14: 1.
13. RICHARDSON, K. C. AND YOUNG, F. G.: *J. Physiol.*, 1937, 91: 352.

INTERACTIONS BETWEEN VARIOUS STEROID HORMONES*

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THE physiology of steroid hormones has long been a subject of great interest both to the physiologist and physician, but it was not until recently when the chemists succeeded in preparing many of these hormones synthetically that really accurate experimentation became possible. It was felt, therefore, that it would be fruitful to make a systematic investigation of the action of synthetic hormone compounds which are free of all contaminations such as were present in the organ extracts used by the earlier workers. This appeared all the more advisable since up to the present time no systematic investigations have been made along these lines outside of a few experiments by Korenchevsky and his co-workers.^{1, 2}

The purpose of the present note is to report on a series of investigations in which synthetic steroid hormone preparations have been given in relatively large doses and over a sufficiently long

period of time to show characteristic changes in the body growth rate and the weight of the various organs. These preparations have either been given alone or in combination with other steroid hormones, and thus it was possible to determine both the action of a single hormone and the manner in which other hormone compounds influence this action. It was found that when given in sufficiently large doses the steroid hormones have a very pronounced effect not only on the sex organs and the endocrine glands but also on the lymph nodes, the kidney, the liver, etc., and on body growth in general, and that in the case of treatment with hormone combinations one active principle may inhibit a certain action of another hormone while its other actions remain uninfluenced or are even enhanced. Since the large scale synthetic manufacturing of steroid hormones makes them readily available for the physician, and since they are already in general use for the treatment of endocrine disorders, it was felt that a brief summary of ex-

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TABLE I.
CHANGES IN THE AVERAGE ORGAN WEIGHTS AND BODY WEIGHTS FOLLOWING TREATMENT
WITH VARIOUS STEROID HORMONES

(All organ weights on this table are expressed in mg. and represent the average of a group of six. The average gain in body weight is expressed in g.)

FEMALES

	Normal	Cholesterol	Estradiol	Progesterone	Testosterone	Desoxycorticosterone acetate	Estradiol + progesterone	Estradiol + testosterone	Estradiol + desoxycorticosterone acetate	Testosterone + progesterone	Testosterone + desoxycorticosterone acetate	Progesterone + testosterone + desoxycorticosterone acetate	Progesterone + testosterone + desoxycorticosterone acetate + estradiol	Formaldehyde + progesterone	Formaldehyde + desoxycorticosterone acetate	Formaldehyde + testosterone
Hypophysis	7.9	7.6	11.0	9.4	6.8	7.0	12.6	8.9	16.2	8.0	6.4	9.7	7.0	7.5	5.9	6.1
Thyroid	13.3	11.8	11.8	15.7	14.2	12.7	12.3	11.9	11.4	12.9	12.8	12.3	11.3	11.4	9.7	9.8
Adrenals	42.0	47.0	48.0	37.7	38.0	36.0	47.0	43.0	45.7	39.0	27.0	33.0	71.0	75.0	57.0	49.0
Thymus	279.0	230.0	33.0	217.4	63.0	216.0	45.0	38.0	64.0	71.0	113.0	53.0	55.0	51.0	53.0	24.0
Heart	669.0	671.0	476.0	557.1	592.0	623.0	538.0	483.0	554.2	579.0	719.0	551.0	583.0	613.0	544.0	530.0
Liver	5281.0	4814.0	4434.0	5493.0	5135.0	5038.0	5621.0	5248.0	5512.0	5124.0	5356.0	5319.0	5324.0	5918.0	4476.0	4624.0
Spleen	1197.0	1082.0	715.0	1407.0	1205.0	1125.0	774.0	966.0	872.0	916.0	1001.0	689.0	749.0	1081.0	567.0	598.0
Kidney	1133.0	1115.0	977.0	1180.0	1242.0	1161.0	1083.0	1199.0	1183.0	1337.0	1539.0	1093.0	1152.0	1179.0	1121.0	1244.0
Lymph nodes	*54.0	47.0	58.0	44.3	55.0	64.0	35.0	39.0	53.0	62.0	49.0	36.0	63.0	87.0	46.0	32.0
Ovary	36.0	31.0	30.0	22.9	25.0	33.0	46.0	40.0	32.0	26.0	22.0	41.0	31.0	29.0	21.0	20.3
Uterus	283.0	260.0	542.0	305.9	556.0	288.0	523.0	436.0	669.0	714.0	488.0	363.0	236.0	266.0	282.0	367.0
Preputial gland ..	49.0	53.0	28.0	20.1	108.0	42.0	35.0	95.0	34.0	101.0	117.0	78.0	41.0	71.0	29.0	72.0
Weight gain	+31.0	+32.0	+11.0	+54.0	+35.0	+35.0	+21.0	+18.0	+18.0	+43.0	+46.0	+26.0	+30.0	+27.0	+30.0	+36.0

MALES

Hypophysis	7.5	7.1	11.0	7.7	6.8	7.9	11.3	8.9	11.5	6.8	6.9	9.8	7.5	9.5	8.5	8.5
Thyroid	18.0	16.3	14.0	17.0	17.0	18.0	15.0	14.0	13.0	13.0	16.0	19.0	13.0	15.0	15.0	17.0
Adrenals	35.0	35.9	48.0	39.0	35.0	40.0	41.0	36.0	39.0	37.0	31.0	46.0	54.0	48.0	55.0	45.0
Thymus	275.0	273.0	103.0	249.0	167.0	180.0	45.0	48.0	42.0	54.0	144.0	50.0	168.0	121.0	112.0	78.0
Heart	755.0	704.0	647.0	727.0	783.0	850.0	641.0	659.9	578.0	680.0	816.0	647.0	727.0	794.0	710.0	763.0
Liver	6215.0	6115.0	5305.0	6272.0	5963.0	6940.0	5821.0	5765.0	5841.0	5230.0	6450.0	6151.0	7926.0	8344.0	7765.0	7515.0
Spleen	1209.0	1179.0	904.0	1344.0	1200.0	1844.0	985.0	942.0	872.0	728.0	1207.0	874.0	1054.0	1059.0	1327.0	1092.0
Kidney	1470.0	1322.0	1237.0	1425.0	1765.0	1676.0	1200.0	1606.0	1375.0	1680.0	1768.0	1656.0	1600.0	1632.0	1589.0	1818.0
Lymph nodes	*39.0	42.0	41.0	47.0	39.0	83.0	51.0	30.0	76.0	29.0	41.0	46.0	44.0	59.0	49.0	35.0
Testis	2527.0	2269.0	645.0	2421.0	1959.0	2327.0	1263.0	2113.0	531.0	2313.0	1811.0	1972.0	2308.0	2277.0	1820.0	1907.0
Seminal vesicles ..	281.0	166.0	55.0	162.0	1017.0	174.0	168.0	1191.0	80.0	1103.0	973.0	1056.0	181.0	112.0	72.0	975.0
Prostate	791.0	576.0	300.0	722.0	1964.0	760.0	537.0	1802.0	290.0	1824.0	1807.0	1769.0	675.0	537.0	397.0	1742.0
Epididymis	698.0	466.0	184.0	560.0	804.0	683.0	361.0	828.0	180.0	786.0	723.0	809.0	691.0	537.0	451.0	754.0
Preputial gland ..	43.0	29.0	23.0	46.0	85.0	58.0	18.0	60.0	66.0	77.0	49.0	62.0	42.0	76.0
Weight gain	+49.0	+48.0	-12.0	+61.0	+26.0	+37.0	-3.0	+6.0	-6.0	-1.0	+33.0	+8.0	+50.0	+45.0	+54.0	+51.0

* In all cases the iliac group of lymph nodes has been prepared and weighed as described by Selye.^s

perimental findings on interrelations between these hormones would perhaps not be out of place in a primarily clinical journal such as this.

After a series of preliminary experiments on various laboratory animals, 192 albino rats, all 7 weeks old, were selected for a final comparative study of the various hormones. Ninety-six of these were females weighing 109 g. and 96 males weighing 154 g. on the average when the experiment was started. The animals of each sex were subdivided into 16 groups of 6. One group remained untreated and served as controls. One group received 6 mg. of cholesterol daily subcutaneously in 0.3 c.c. of peanut oil. This group was supposed to show the effect of a hormonally inactive sterol when given in an amount corresponding to the maximum dose used in any of the hormone combination experiments. The other groups received various hormones alone or in combination with each other. Estradiol was given in daily doses of 300 gamma progesterone, testosterone and desoxycorticosterone acetate in daily doses of 2 mg. The daily dose of each of these compounds was dissolved in 0.1 c.c. of peanut oil and injected subcutaneously. Since our previous experiments have shown that non-specific damaging agents such as toxic doses of various drugs exert a pronounced influence on certain endocrines, especially the adrenals³ and the gonads⁴ we include one group in which non-specific damage was caused by three daily injections of 0.2 c.c. of a 4 per cent formaldehyde solution, the dose being raised during the last week of the experiment to three times 0.3 c.c. In three other groups we studied the action of progesterone, testosterone and desoxycorticosterone acetate, respectively, concerning their ability to influence the non-specific actions of formaldehyde. The experiments were carried on for 21 days, at the end of which period all animals were weighed, killed, and, after careful dissection, their organs were weighed on an analytical balance. The accompanying table summarizes our findings.

We have also made a histological study of the organs enumerated in the table in order to determine the structural changes responsible for the variations in gross weight. While it is impossible to comment on all these findings in a short preliminary report such as this, we should like to point out a few of the more interesting results.

It will be seen that estradiol causes marked

atrophy of the gonads in the males and to a lesser degree also in the females, but this effect is inhibited to some extent in the male by progesterone, while in the female the average ovarian weight in animals receiving progesterone in combination with estradiol is actually above normal. This confirms our previous observations in the mouse.⁵ Testosterone also inhibits the gonadal atrophy caused by estradiol in both sexes. This is all the more remarkable since both progesterone and testosterone tend to cause gonadal atrophy when given by themselves. The weight of the kidneys is increased by testosterone and decreased by estrin. The most marked increase in the size of the kidney was observed both in the male and in the female group when testosterone and desoxycorticosterone were given in combination. This may be of practical significance inasmuch as it has been shown⁶ that the enlarged kidney of testosterone treated animals is functionally superior to that of untreated controls, in so far as it is more resistant to the action of kidney damaging drugs, *e.g.*, sublimate. The adrenals are greatly enlarged in the estradiol-treated animals of both sexes, while testosterone, especially when given in combination with desoxycorticosterone, causes a decrease in their size which upon histological examination proves to be due to cortical atrophy. The non-specific adrenal enlargement caused by formaldehyde is only slightly inhibited by desoxycorticosterone in the female and not at all in the male. Testosterone, on the other hand, markedly inhibits this enlargement in both sexes. Since testosterone also tends to raise the general resistance of experimental animals this finding seems of importance as a possible lead for the study of the influence of steroid hormones on the response of the organism to non-specific damage, a response in which adrenal enlargement plays an important part. The average gain in body weight during the three weeks of the experiment was by far greatest both among the males and among the females in the groups receiving progesterone. Testosterone alone and in combination with desoxycorticosterone or progesterone likewise seems to stimulate body growth in females but not in males. This latter observation supports and extends the previous findings of McEuen, Selye and Collip,⁷ who showed that testosterone stimulates body growth in females, a fact which has since been confirmed by several investigators.

The expenses of this investigation were defrayed through a grant in aid received from the Schering Corporation, of Bloomfield, N.J. The author is especially indebted to Drs. G. Stragnell and E. Schwenk of the above Corporation for the synthetic hormones used in these experiments, and to Miss L. Bassett and Messrs. K. Nielsen, H. Torunski and C. Rasmussen of this Department for technical assistance.

REFERENCES

1. KORENCHEVSKY, V., HALL, K. AND BURBANK, R.: The manifold effects of prolonged administration of sex hormones to female rats, *Biochem. J.*, 1939, 33: 372.
2. KORENCHEVSKY, V., HALL, K. AND ROSS, M. A.: Prolonged administration of sex hormones to castrated rats, *Biochem. J.*, 1939, 33: 213.
3. SELYE, H.: Studies on adaptation, *Endocrinol.*, 1937, 21: 169.
4. *Idem*: The effect of adaptation to various damaging agents on the female sex organs in the rat, *Endocrinol.*, 1939, 25: 615.
5. SELYE, H. AND STEVENSON, J.: The toxic effect of oestrogens as influenced by progesterone, *Canad. Physiol. Soc. Meeting, Kingston, 1939*, this issue of the *Canad. M. Ass. J.*, p. 190.
6. SELYE, H.: On the protective action of testosterone against the kidney-damaging effect of sublimate, *Montreal Physiol. Soc., December, 1939*. (See also this issue of the *Canad. M. Ass. J.*, p. 189.)
7. McEUEEN, C. S., SELYE, H. AND COLLIP, J. B.: Effect of testosterone on somatic growth, *Proc. Soc. Exper. Biol. & Med.*, 1937, 36: 390.
8. SELYE, H.: Thymus and adrenals in the response of the organism to injuries and intoxications, *Brit. J. Exper. Pathol.*, 1936, 17: 234.

THE CONTRIBUTION OF THE ELECTRON MICROSCOPE TO MEDICINE

(I. THE ELECTRON MICROSCOPE DESCRIBED)

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THE microscope is an instrument peculiarly serviceable to the biologist and the medical scientist. Its early developments, in England at any rate, were in the hands of the natural scientists, and even today, if one wants the best technique in the use of a microscope, one is inclined to turn to the biologist rather than to the physicist. The biologist is a specialist in using the instrument and is not concerned overmuch with the theory; the physicist very often can reel off pages of mathematical theory regarding the working of the instrument but would often find great difficulty in setting one up for actual use. With the electron microscope both the technique and the theory are of a new type and the trained physicist is indispensable.

1. LIMITATIONS OF THE ORDINARY MICROSCOPE

When one examines the geometrical drawing showing the method of formation of the image in the ordinary compound microscope (Fig. 1b), one can see no apparent reason why the magnification produced should not be made greater and greater merely by enlarging the dimensions of the instrument. This appears possible because we represent the light by rays, i.e., we treat the light as though it were propagated exactly in straight lines. However, such is not the case. Light has the characteristics of a wave motion and can consequently bend around obstacles, a phenomenon which becomes very important when the obstacle becomes extremely small.

Ordinary light is just an electromagnetic

wave similar in many particulars to the waves employed in wireless telegraphy. The difference is in the wave-length. Whereas wireless waves have wave-lengths of the order of 100 metres and we receive the signals in our radios, light has a wave-length of from four to ten-millionths of a metre, and we receive such signals on the retina of our eyes, or on a photographic plate. However even such short wave-lengths are considerably larger than the linear dimensions of many bodies in which the microscopist is interested. It is this fact that sets a minimum to the size of particles made visible to us by the microscope.

The essence of microscopic vision is to reproduce in an image on the retina, or on a photographic plate, a replica of an object with the essential fine structures in the object separated in the image; that is, we wish to see greater and greater detail in the object. Satisfactory performance of the instrument is judged by its ability to depict for us very fine points or fine particles present in the object. On account of the fact that light is a wave motion it is impossible for any instrument to separate in an image two fine particles of an object if those particles are really closer together than the wave-length of the light used. This means that no microscope can be constructed to be used with ordinary light that will enable us to see in detail a particle less than about two one-

hundred-thousandths, $\frac{2}{100,000}$ ths of a cm. (0.2 μ or 0.2 microns), in diameter, or a fibre or thread less than this amount in cross-sectional diameter.

This lower limit can be extended to smaller

magnitudes if ultra-violet light, the wave-length of which may be less than one-half the average wave-length of visible light, is used. The microscope devised by Barnard and Gye (about 1925) made use of ultra-violet light, and they were able to improve microscopic images to a certain extent. However, the magnification they attained was only double the old.

2. X-RAYS AND ELECTRONS

Scientists have always fostered the hope that a form of radiation would some day be discovered which would have a much shorter wave-length and consequently might lend itself to photographing in detail still smaller objects. In the last decade of the nineteenth century both electrons and x-rays were discovered and the question arose as to whether these might not lead to a solution of the problem.

On account of their effect on a photographic plate and their power to penetrate matter, x-rays were from the first thought to be a form of light, but all attempts to make x-rays amenable to refraction by any kind of lens failed. They have proved to be of the greatest use in depicting the intimate structure of crystals but this is due to phenomena not directly related to microscopic vision.

One reads so much about electron tubes and the miracles that can be performed with them through engineering developments, that electrons seem to be very familiar to us. They can be produced in so many ways that we have come to look upon them as one of the primary constituents of all matter. From the time of their first discovery over forty years ago they have been looked upon as very minute, negatively-charged particles moving in clouds or streams, often with a great velocity, which may even approach the velocity of light.

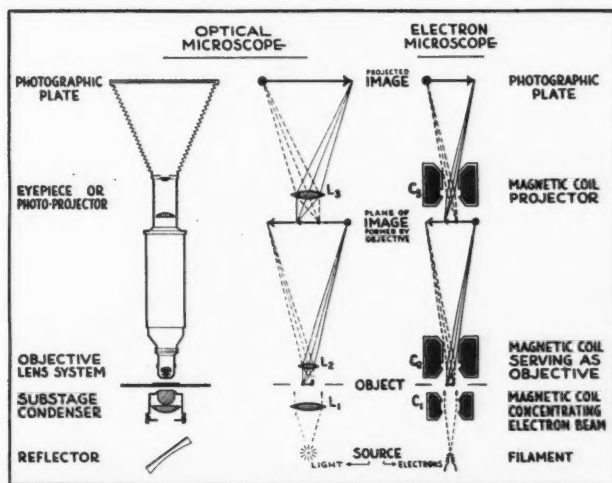


Fig. 1a

Fig. 1b

Fig. 1c

3. RELATIONSHIP BETWEEN LIGHT AND ELECTRONS

During the present century our views regarding the true nature of light have changed greatly. In some experiments, as for example with the microscope, light acts as though it were merely a wave-motion. In other experiments, *e.g.*, the photoelectric cell, we must regard light as corpuscular in nature—a beam of light, according to this view, being a stream of discrete bundles of energy to which the name photons has been given.

When this duality of light became evident to the physicist, he began to enquire whether

TABLE I.
CONTRAST BETWEEN LIGHT AND ELECTRON MICROSCOPES. (SEE FIG. 1)

Elements	Light microscope	Electron microscope
1. Source of illumination.	Sunlight or electric light.	Electron source: cold cathode or hot filament.
2. Control of illumination.	Sub-stage condenser, L_1 .	Converging action of the magnetic field of the first coil, C_1 .
3. Specimen support.	Microscope slide of glass about 1 mm. thick.	Film of collodion about 10 millimicrons thick.
4. First image forming system.	The objective, L_2 .	Converging action of the magnetic field of the second coil, C_2 , forming the first image.
5. Accessory magnification.	The eyepiece or photographic projector, L_3 .	Converging action of the magnetic field of the third coil, C_3 , forming a second enlarged image of a portion of the first image.
6. Medium.	Air and glass.	A very high vacuum.
7. Viewing image.	The eye directly.	The eye (image projected on fluorescent screen).
8. Method of focussing.	Movement of lenses as a result of judging the sharpness of the image with the eye.	Alteration of the intensity of the magnetic fields in the coils as a result of judging the sharpness of the image on a fluorescent screen.
9. Recording of image.	Photographic plate.	Photographic plate.
10. Smallest particle photographed in detail.	2 100,000 cm.	Even less than 1 1,000,000 cm.

similar duality should not be ascribed to the electron beam. Our first conception of an electron beam was that it consisted of a stream of small negatively charged corpuscles, each particle having a mass about $1/2,000$ th of that of a hydrogen atom. In 1925 it was shown experimentally that an *electron beam displayed the same dual nature displayed by light*. Consequently, an electron beam must sometimes be looked upon as a wave-motion. Moreover its wave-length is only a very small fraction of that of ordinary light. The question arose: "Can we have an electron microscope?" and "Will it enable us to see particles or structures much finer than the ordinary microscope can?" The answer to both questions is "Yes". It is now possible to photograph particles smaller than ten millimicrons ($10\text{ m}\mu$ or one-millionth of a cm.) and likewise to see in microscopic objects details which are many times finer than those made visible by the most powerful light microscope.

4. THE USE OF AN ELECTRON BEAM

The essential principle underlying the operation of an ordinary microscope is the bending of the rays of light emanating from an illuminated object by a system of glass lenses so that the rays produce an image on the photographic plate (or the retina of the eye). In the electron microscope this essential feature of the action of a glass lens on light is performed by the action of a particular type of magnetic field on the beam of electrons. That is, *a type of magnetic field has been discovered which has the same effect on a beam of electrons, as a glass lens has on a beam of light* (Figs. 1b and 1c).

5. COMPARING LIGHT AND ELECTRON MICROSCOPES

The accompanying table sets out the contrasts and similarities between the light microscope and the electron microscope (see Fig. 1).

6. PRECISE DESIGNATION OF MAGNIFYING POWER

In both the electron microscope and the light microscope the detail which is visible in the final image is determined by the objective lens. In each case the objective produces an image which contains all the detail that will be visible in the final picture. However, the image produced by the objective is seldom at a magnification of more than $\times 100$ in either instrument and hence most of the detail present still cannot be seen by the eye. The subsequent magnification by the eye-piece in the case

of the light microscope, and the projector coil in the case of the electron microscope, merely serves to increase the dimensions of these details until they are visible to the eye. In order to be visible, the finest detail of the picture must be larger than 0.02 cm . A simple calculation shows that in the case of the light microscope an eye-piece magnification of $\times 10$ is necessary, thus bringing the total magnification up to $\times 1,000$; in the case of the electron microscope the second magnification must be considerably over $\times 200$ in order to produce a final

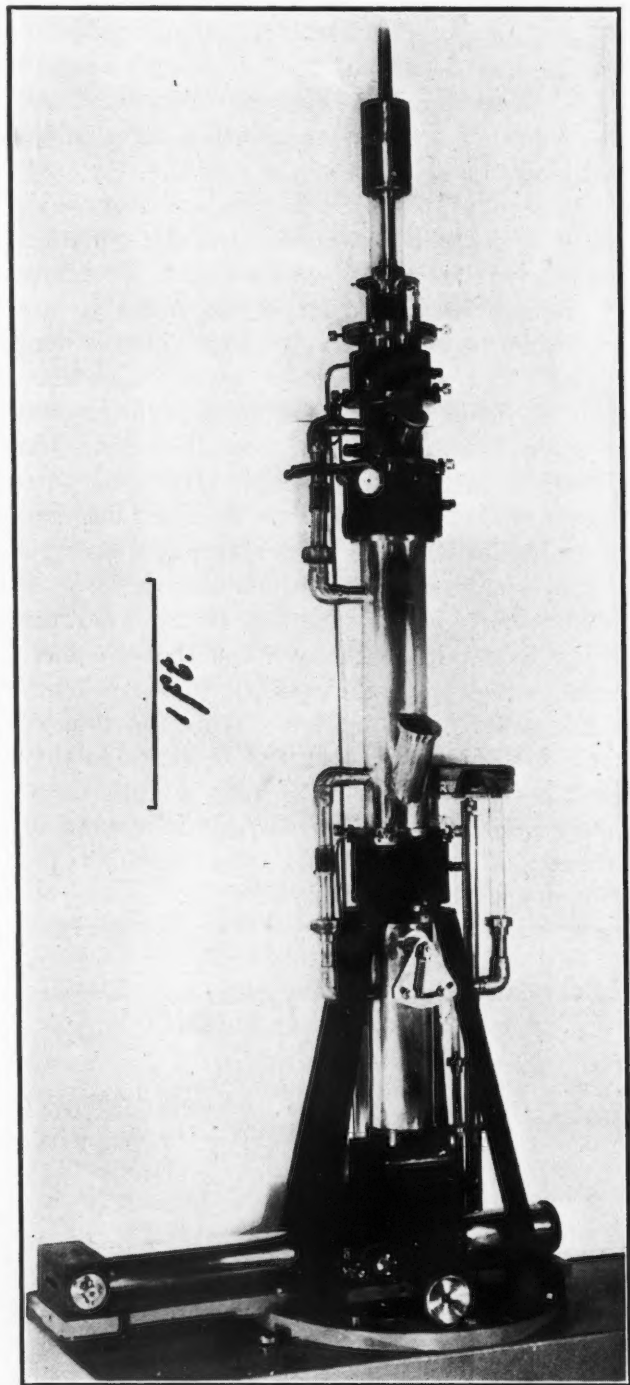


Fig. 2.—Photograph of electron microscope.

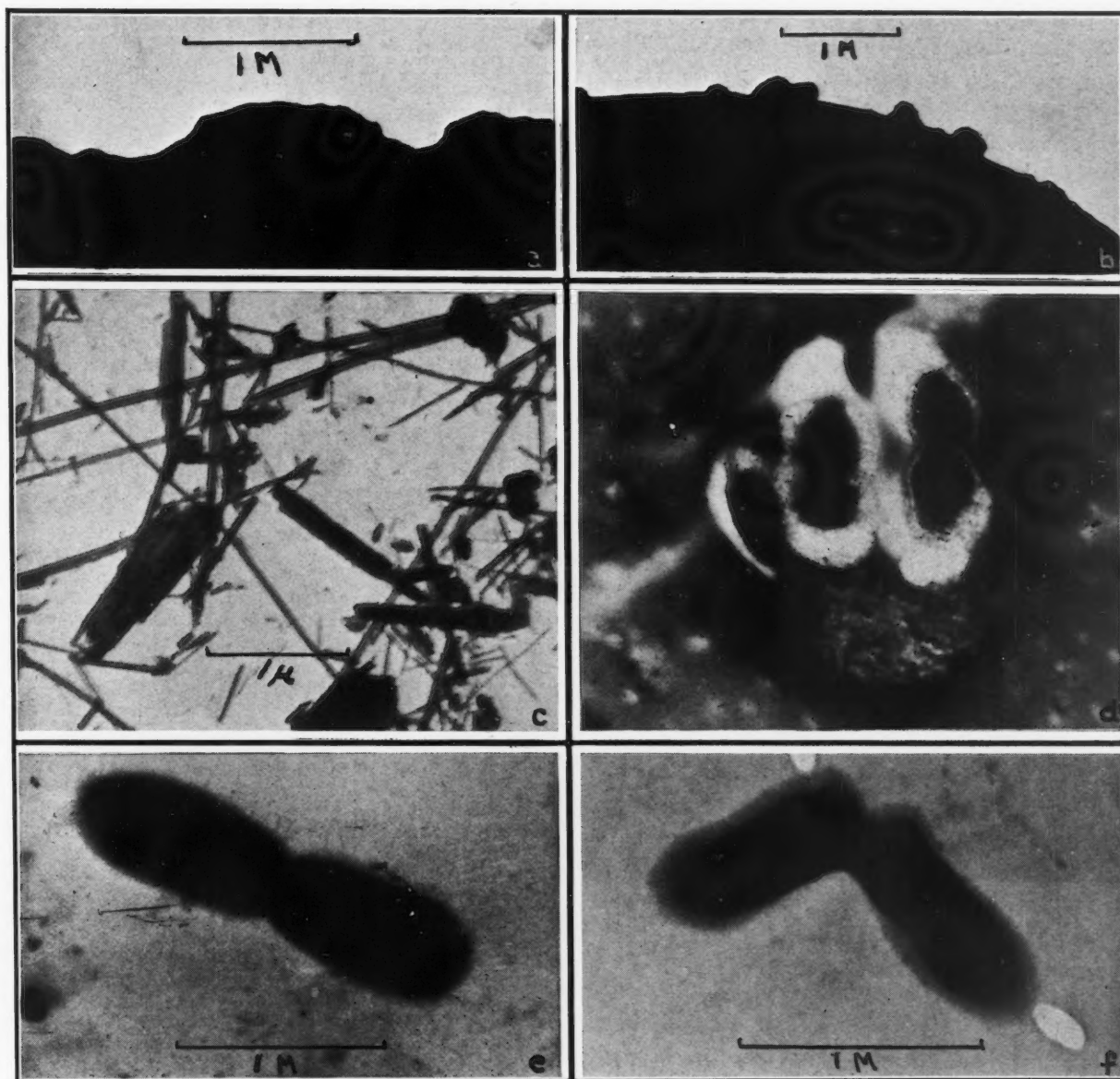


Fig. 3a.—Portion of edge of new razor blade about $1/8,000$ of an inch. $\times 24,000$. Fig. 3b.—Edge of a pollen particle from *Cupressus sempervirens*. $\times 16,000$. Fig. 3c.—Small fibres of asbestos making up asbestos dust. $\times 19,000$. Fig. 3d.—Group of pneumococci from peritoneal fluid of a dead mouse. $\times 18,000$. Fig. 3e.—Method of division of a *B. prodigiosus*. $\times 28,000$. Fig. 3f.—Method of division of diphtheroid bacillus. $\times 33,000$. In each cut the straight line represents $1\mu = 0.0001$ cm.

magnification of $\times 20,000$ or over. We may call these final numbers $\times 1,000$ and $\times 20,000$ the respective magnifying powers of the instruments, since further magnification, in either case, would reveal no more detail to the eye. For practical reasons, a large number of photographs taken with the electron microscope are taken at magnifications near $\times 12,000$. Hence, there is considerable detail on the plates that is still invisible to the eye. In order to make this detail visible, it is necessary to enlarge the photographs optically until the total magnification is over $\times 20,000$.

Often, to overcome difficulties of reproduction or demonstration, it is necessary to enlarge the photograph to a total magnification con-

siderably above this value. This subsequent magnification has no physical significance.

The photographs given in this and succeeding papers will all be marked by a number representing the final magnification. Each reproduction will be accompanied by a line indicating the scale; thus $\text{———} 1\mu$, the symbol μ being one ten-thousandth of a centimetre.

7. SAMPLES OF RESULTS OBTAINED WITH THE ELECTRON MICROSCOPE

In Fig. 3 (a to f) are shown some typical results obtained so far with the electron microscope. The legend attached explains these sample results.

SARCOMA OF THE PROSTATE*

(WITH REPORT OF A CASE OF RHABDOMYOSARCOMA)

BY H. E. TAYLOR, M.D., C.M. (DAL.)

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SARCOMA of the prostate is rare in comparison with carcinoma. Lowsley and Kimball¹ reviewed the literature in 1934 and found 131 cases, to which they added one of their own; Stirling and Ash² in 1938 added 40 other reported cases, and described 5 new ones. Many varieties have been reported, no less than 19 having been mentioned in the literature. According to Lowsley and Kimball the round-cell type comprises 30 per cent of the cases, spindle cell 19 per cent, myxosarcoma 8 per cent, leiomyosarcoma and rhabdomyosarcoma 7 per cent, and other types in smaller percentages. Such neoplasms may arise at any age, the youngest reported being 4 months, the oldest 88 years. The majority, however, are found in youth, the highest percentage being in the first decade. Ewing³ claims that many so-called sarcomas are actually very anaplastic carcinomas.

Malignant tumours arising from striated muscle, *i.e.*, rhabdomyosarcomas, are curiously rare (Boyd⁴). Approximately 50 per cent of the pure type arise in the genito-urinary tract. They can be definitely diagnosed histologically because of the presence of cross striations, though in very anaplastic growths only a small proportion of the cells show this feature. Fouchar⁵ states that the primary rhabdomyosarcoma of the prostate probably arises from a wedge-shaped portion of the gland situated behind the pubic bones and between the lateral lobes and which contains bands of striped muscle. Because of the rarity of this type of tumour and its importance from a diagnostic standpoint, the following case is reported.

CASE REPORT

J.S., male, age 55 years, unemployed, was admitted to the Glasgow Royal Infirmary on January 20, 1939, complaining of suprapubic pain which had been present since the previous November; this had been accompanied by pain, heat and swelling of the left testicle. At the commencement of the illness he had had difficulty in urination, but when admitted this had improved. There was nothing of importance in his past history. On rectal examination a large, irregular, soft mass was felt anteriorly; it was not tender. There was no distension of the bladder and no enlargement of either testicle.

* From the Department of Pathology of the University and Royal Infirmary, Glasgow.

The only abnormality in the urinalysis was the presence of many pus cells in the sediment. The blood urea was 31 mg. per cent. X-ray of the pelvic bones showed no abnormality. A suprapubic prostatectomy was performed on February 1st by Mr. G. Stevenson. The prostate was found to be greatly enlarged and soft. Enucleation was impossible and portions sufficient to fill a small "kidney dish" were removed piecemeal. Recovery was uneventful, and by March 7th the wound was practically healed and the patient was passing urine normally. He was discharged, improved, on March 12th. Histological examination of the tissue showed it to be a very anaplastic sarcoma.

On March 27th he was readmitted, complaining of difficulty with micturition and rigors of a few days' duration. The suprapubic wound was suppurating and the urine was loaded with pus. Rectal examination showed the tumour to be disseminated throughout the pelvis. He gradually declined, and died on April 20, 1939.

Post-mortem examination.—The body was that of a very emaciated adult male. A suprapubic opening connecting with the bladder was present, the walls of which showed advanced suppuration and sloughing but no obvious evidence of tumour growth.

The lungs were markedly anthracotic; no metastases were found in them after a careful search. The heart showed an early stage of brown atrophy. No metastases were present in any of the abdominal viscera.

The pelvis was filled with tumour tissue which had apparently arisen from the prostate gland and had infiltrated the perirectal and perivesical tissues, thus forming a large mass in which the rectum, bladder and prostate were incorporated. This mass was so firmly adherent to the pelvic walls that it could be removed only by dissection with a scalpel. On section the tumour tissue had a grey-white colour, was of a soft friable consistency, and was cut with ease. On opening the bladder it was found to be markedly contracted and the mucous membrane was covered with a dark-coloured, foul-smelling slough. The prostatic bed was filled with tumour tissue, and at one point this was infiltrating the bladder wall. The neighbouring lymph glands were free from tumour. The testicles were normal. Examination of the femurs, ribs and vertebrae revealed no metastases. The kidneys showed a bilateral ascending pyelonephritis.

Histology of the tumour.—Several blocks were taken from various parts of the tumour for examination. The sections showed a very cellular tumour composed mainly of spindle-shaped cells which, in many places, were arranged in interlacing bundles (Fig. 1). It had a fairly rich blood supply, the vessels being very thin-walled, but hæmorrhage was not marked. In one section myxomatous change and a small area of necrosis were present. No normal prostatic tissue was seen in any of the sections taken at autopsy, though this was present in the biopsy specimen. The majority of the cells composing the above-mentioned bundles had well-stained nuclei, which were short and thick, with rounded ends; the cytoplasm was scanty and stained poorly with eosin. Scattered amongst these cells were others with similar nuclei but whose cytoplasm stained deeper with eosin. In other areas the cells were pleomorphic; some were small and round, others oval, while still others were very large and multinucleated. These cells also varied as to the amount of cytoplasm present; the larger the cell, the more eosinophilic was the cytoplasm (Fig. 2). Mitosis was present in many cells. Sections from all blocks were studied by Heidenhain's iron hæmatoxylin

stain and an oil-immersion lens. In one section cross striations were demonstrated in occasional cells (Fig. 3); these appeared to be of the larger type, with the rich cytoplasm seen in the hæmatoxylin and eosin sections. The presence of the cross striations in the more differentiated cells conclusively proved this tumour to be an anaplastic rhabdomyosarcoma.

DISCUSSION

Bumpus⁶ states that sarcoma is the probable diagnosis in every case of prostatic tumour in patients below the age of forty years. The onset is usually insidious and its course is rapid, the average duration of life being only nine months (Lowsley and Kimball). The patient reported above lived seven months from the onset of the first symptom. The younger the patient, the more rapid is the course. Pain is nearly always

simulating benign adenoma, although in the present case the growth was very diffuse. The tumour pushes the bladder up and forwards, thus causing obstruction to the urethral orifices and urethra, as a result of which there is a partial or complete retention of urine, accompanied by an ascending infection which may prove fatal; in fact, Stirling and Ash contend that the majority of these patients die of an intercurrent infection, *e.g.*, pyelonephritis or pyonephrosis, more frequently than of the tumour *per se*. The absence of metastases in the above case can probably be accounted for by the fact that the pyelonephritis hastened his death before the tumour had time to disseminate.



Fig. 1

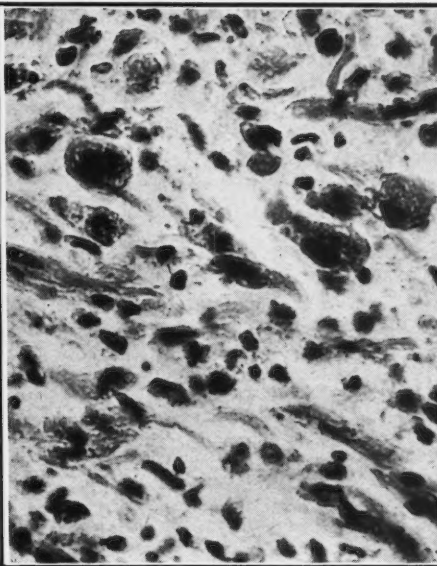


Fig. 2



Fig. 3

Fig. 1.—Bundles of spindle-shaped cells arranged in interlacing fasciculi. Some are cut across and appear as round cells. H. and E. x 75. Fig. 2.—Note the pleomorphism and large cells with the rich eosinophilic cytoplasm. H. and E. x 250. Fig. 3.—Young muscle cell showing cross striations. Heidenhain's iron-hæmatoxylin. x 1,000.

present; this may be suprapubic, as in this case, or in the rectum and perineum, or along the line of the sciatic nerve. There are usually marked cachexia and secondary anæmia. Rectal examination frequently reveals a smooth, tense, symmetrical tumour which is soft or balloon-like in consistency, thus simulating an abscess, for which it is most frequently mistaken; in other cases it is smooth and firm, but never so hard and fixed as a carcinoma. The size of the growth varies from a small nodule to a large mass entirely filling the pelvis; in one case it extended up to the umbilicus (Gilbert⁷), in others it causes protrusion of the perineum. The rhabdomyosarcomas reported in the literature are most frequently well-circumscribed and firm,

The most useful method for an accurate diagnosis is stated to be the aspiration biopsy; according to Stirling and Ash this is diagnostic in 80 per cent of cases and is extremely valuable in differentiating a sarcoma from an abscess or a carcinoma.

Dissemination of the growth varies with the type of tumour present. The round-cell and spindle-cell varieties are the most malignant, causing early infiltration of the bladder and rectum, and occasionally involvement of the penis and scrotum. Spread to the neighbouring lymph glands occurs in 76 per cent of all cases (Lowsley⁸). Smith and Torgeson⁹ state that in 40 per cent of the cases distant metastases are found, and that the organs most frequently in-

volved are the bones (ribs and vertebræ), lungs, kidneys, liver and pleuræ, in that order. In the case reported here no metastases were found.

On account of the varied histological characters many terms have been applied to these sarcomata of the prostate, *e.g.*, spindle-cell, round-cell, mixed-cell, myxosarcoma, rhabdomyosarcoma, etc. This is partly due, as in the above case, to the very complex cell-picture present, the histology varying in sections from different parts of the tumour. In the present instance myxomatous change predominated in some sections, in others spindle-cells, and in still others marked pleomorphism of the cells. It was only by a close study of many sections that the true diagnosis was reached. It is thus essential that a number of blocks be examined from different parts of the tumour. The presence of large bundles of cells with strongly eosinophilic, rather elongated, cytoplasm is suggestive of a rhabdomyosarcoma, but for a definite diagnosis to be made cross striations must be demonstrated. This is especially difficult in undifferentiated tumours, such as the one reported, where the striated myoblasts were seen in only one of the many sections examined.

TREATMENT

Because of the very malignant nature of these neoplasms the clinician rarely sees the patient

sufficiently early for radical surgery, *i.e.*, total prostatectomy, to be of benefit, although surgical intervention is indicated in the treatment of the urinary obstruction and its complications, so often present. Gilbert, who reviewed the literature to determine the value of radiation methods in treating this disease, states that the use of vigorous radium and deep x-ray therapy gives a slight degree of clinical control in some cases; several have been reported living from two to six years following this type of treatment in patients over 40 years of age. The majority, however, merely show a temporary improvement.

My thanks are due to Mr. G. Stevenson for permission to use his clinical records, and to Professor J. W. S. Blacklock for his kindness in helping me with the preparation of the paper.

REFERENCES

1. LOWSLEY, O. S. AND KIMBALL, F. N.: Sarcoma of the prostate, *Brit. J. Urol.*, 1934, 6: 328.
2. STIRLING, W. C. AND ASH, J. E.: Sarcoma of the prostate, *J. Urol.*, 1939, 41: 515.
3. EWING, J.: *Neoplastic Diseases*, Saunders, N.Y., 1928.
4. BOYD, W.: *Textbook of Pathology*, Lea & Febiger, Phila., 1938.
5. FOUCAR, F. H.: Rhabdomyosarcoma of the prostate, *Am. J. Path.*, 1935, 11: 753.
6. BUMPUS, H. C.: Radium and roentgen-ray in the treatment of sarcoma of the prostate, *J. Urol.*, 1925, 14: 519.
7. GILBERT, J. B.: Sarcoma of the prostate, *ibid.*, 1934, 32: 63.
8. LOWSLEY, O. S.: Sarcoma of the prostate, *J. Am. M. Ass.*, 1934, 103: 983.
9. SMITH, R. R. AND TORGESON, W. R.: Sarcoma of the prostate, *Surg., Gyn. & Obst.*, 1926, 43: 328.

HEREDITARY JAUNDICE IN THE RAT

BY HELGA TAIT MALLOY* AND LOUIS LOWENSTEIN

Montreal

THE jaundiced rats described in this paper first occurred as a mutation in the stock of Wistar albino rats in the Connaught Laboratories in Toronto. Gunn,¹ who discovered them, showed the subsequent inheritance of the jaundice to be of Mendelian recessive character. The jaundice occurs in the expected ratio in a significant number of mixed matings, and when both parents are jaundiced all the offspring are jaundiced. Because of the hereditary nature of the disease and the fact that the bilirubin in the serum is invariably of the indirect type, Gunn suggested an analogy with hereditary hæmolytic jaundice in the human subject. This was further supported by his finding of an increased

fragility of the red cells in hypotonic saline. This observation we were unable to confirm and the investigation outlined in this paper finally resolved itself into an attempt to discover the cause of the jaundice. With this end in view the possibilities of the jaundice being caused by an excessive destruction of red cells or by an impairment of bilirubin excretion were investigated in order.

RESULTS

Blood picture.—Table I shows the blood picture of 20 normal and 20 jaundiced rats weighing between 200 and 250 grams, fed on a diet of purina biscuits, supplemented once weekly with lettuce and carrots. To save space, only the mean of the normals is shown. The rats

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were free from infection, and had not been bled for other purposes for at least a month previously. Under these conditions the hæmoglobin level, red cell counts, and hæmatocrit readings on the normal control rats are about 10 per cent lower than those reported by Higgins and Stasney² for normal rats. All but four of the jaundiced rats show an anæmia and an accompanying reticulocytosis when compared with the normal controls.

TABLE I.
HÆMOGRAMS OF JAUNDICED RATS
AND NORMAL CONTROLS

Hgb.	R.B.C.	C.I.	Retic.	Ht.	M.C.V.	W.B.C.	Bili- rubin
gm. %	10 ³ /mm. ³		%	%			mg. %
NORMAL RATS							
16.0	8,200	62	3	45	55	15,000	0
JAUNDICED RATS							
15.1	8,400	58	6	48	57	15,500	4.5
14.1	7,650	59	9	47	61	17,000	5.0
16.5	9,240	57	2	47	51	13,200	5.0
15.3	8,600	57	8	46	56	12,800	6.2
15.6	8,550	58	6	48	54	16,000	7.0
14.5	7,270	64	11	41	56	11,430	6.3
14.8	6,100	78	13	38	62	16,800	6.1
15.4	7,530	65	10	45	59	8,800	5.9
14.2	5,750	78	17	40	69	10,000	7.0
15.4	6,890	70	9	45	65	15,200	5.3
14.2	8,260	55	12	39	47	12,300	6.2
14.2	7,720	59	10	39	51	11,780	7.5
14.0	7,870	57	15	43	54	17,900	6.2
14.0	6,665	67	11	38	55	11,000	7.2
15.6	8,200	64	6	46	56	17,000	7.1
16.0	8,200	62	4	45	55	13,340	4.8
15.6	8,550	59	3	48	56	12,900	6.2
13.8	5,890	75	14	40	68	16,200	6.7
15.8	8,000	63	2	46	57	14,000	5.9
16.0	8,400	61	3	48	57	15,500	6.1

Hgb.; hæmoglobin, determined by the method of Evelyn.⁶ R.B.C., red blood cells. C.I., colour index. Retic., percentage of reticulocytes in 500 red blood cells, by brilliant cres 1 blue, dry mount technique. Ht., hæmatocrit. M.C.V., mean corpuscular volume. W.B.C., white blood cells. Bilirubin, determined by a micro modification of the method of Malloy and Evelyn.⁷

The lowest recorded hæmoglobin level is 13.8 grams per cent and the highest reticulocyte count is 17 per cent. On the whole, it can be seen that the degree of reticulocytosis bears a fairly close relationship to the degree of anæmia. No significant deviation from normal is seen in the colour-index, the mean corpuscular volume, or in the number of white cells. Bilirubin levels of 4.5 to 7.5 mg. per 100 c.c. of plasma are observed but no obvious correlation can be seen between the degree of anæmia and the degree of bilirubinæmia. The bilirubin is invariably indirect in type.

Measurement of the diameter of the red cells revealed no significant difference between the normal and the jaundiced rats.

Red cell hæmolysis.—No difference in the fragility of the red cells in hypotonic saline was detected between the normal and the jaundiced rats. When the cells were suspended in hypertonic saline followed by dilution in water, according to the method of Murray,³ the cells from normal and jaundiced rats again behaved in an identical manner. No difference in the rate of hæmolysis with staphylococcus toxins α and β could be detected.

Curves A and B, Chart 1, show the increased resistance of washed red cells of jaundiced rats towards hæmolysis by saponin when compared with the washed red cells of normal rats. Curves C and E show the protective action which normal rats' serum exerts in saponin hæmolysis and curves D and F show the even greater protection afforded by jaundiced rats' serum.

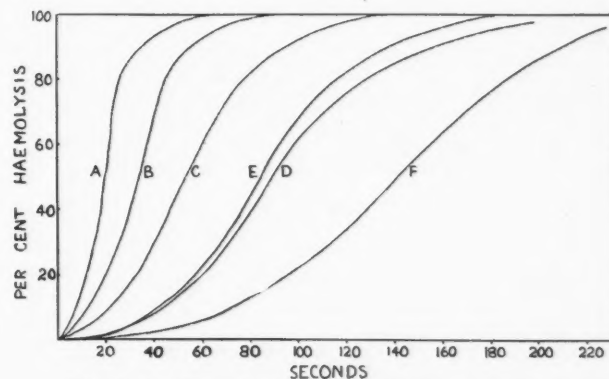


Chart 1.—Hæmolysis with saponin. A saponin concentration of 1/10,000 was used in each experiment. The rate of hæmolysis was determined on the Evelyn photoelectric colorimeter with filter 660, at which wavelength hæmoglobin does not interfere. A, normal red cells. B, jaundiced red cells. C, normal red cells with normal serum. D, normal red cells with jaundiced serum. E, jaundiced red cells with normal serum. F, jaundiced red cells with jaundiced serum.

Splenectomy.—Gunn^{1, 4} reported that splenectomy performed on bartonella-free jaundiced rats did not cure the jaundice. Our attempt to confirm his observation on eight jaundiced rats resulted invariably in the death of the animal from bartonella infection within four or five days after the operation.

Post-mortem examination.—Autopsies performed on the jaundiced rats revealed a marked yellow tint of the skin and connective tissue. The muscles, lymph nodes, stomach, intestine, pancreas, heart and lungs, and the adrenal, parathyroid and pituitary glands were normal in appearance, except for a slight icteroid tint,

much less marked than in the skin. The liver and kidneys were dark in colour but otherwise appeared normal. The spleen was also dark and distinctly smaller than normal. Marked deposition of an almost black pigment was seen in the thyroid and in Harder's gland. The distribution of the bone-marrow was normal, being present in all the long bones except the radius and ulna. The bone-marrow was of ordinary greyish-red colour, not fatty, and not obviously hyperplastic. On microscopic examination no divergence from the normal was detected in the liver, spleen, or bone marrow, either in fixed preparations stained with hæmatoxylin and eosin or in the fresh tissue stained supravitaly.

Since no direct evidence emerged from the above observations which pointed to a hæmolytic

removing the liver just prior to injection. This result provides the first real clue to the cause of jaundice in the jaundiced rat.

In experimental bilirubin retention in the normal rat, produced by tying the bile duct, part of the injected bilirubin appears as direct bilirubin in the serum, shown in heavy shading in Chart 2. This does not occur in the hepatectomized rat nor in the jaundiced rat, which leads to the conclusion that some abnormality of the liver of the jaundiced rat prevents direct bilirubin formation. This is suggestive as a second possible clue to the cause of jaundice in the jaundiced rats. Since only direct bilirubin is found in urine and in fresh bile it seems logical to assume that its adequate formation is an essential precursor to bilirubin excretion. Hence

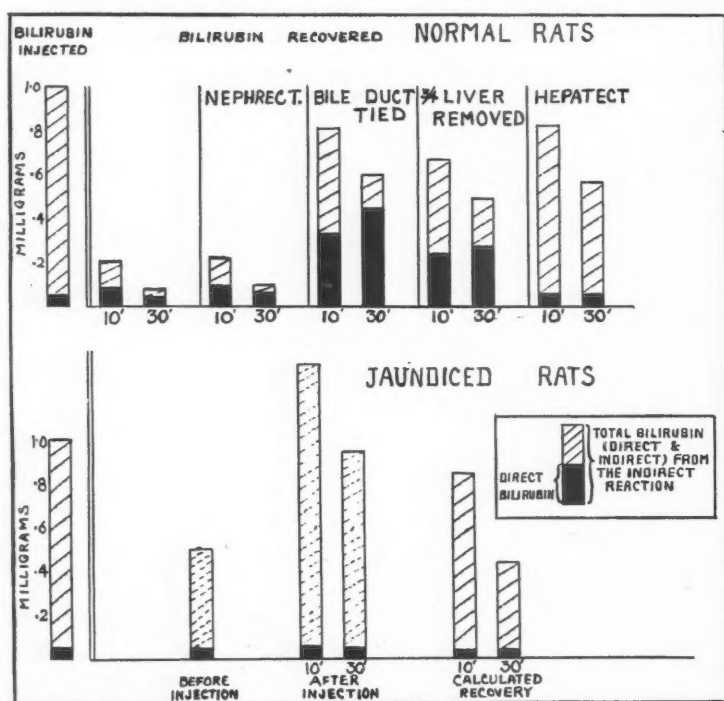


Chart 2

Chart 2.—Recovery of injected bilirubin. Bilirubin determinations (7) were done on plasma drawn in 10 and 30 minutes after injection. The total recovery was calculated from the plasma volume, assuming a 200 gram rat to have a plasma volume of 10 c.c. The operations on the normal rats were performed immediately preceding the injection. Light ether anaesthesia was used throughout. **Chart 3.**—Bile-duct occlusion.

process being responsible for the jaundice, attention was directed to the ability of the rats to excrete bilirubin.

Bilirubin injection.—Chart 2 shows the result of injecting 1 mg. of bilirubin into normal and jaundiced rats. It can be seen that the jaundiced rats are unable to excrete bilirubin at the normal rate. In fact the curves of bilirubin retention in the jaundiced rats bear a close resemblance to those obtained from rats in which excretion had been made impossible by tying the bile duct or

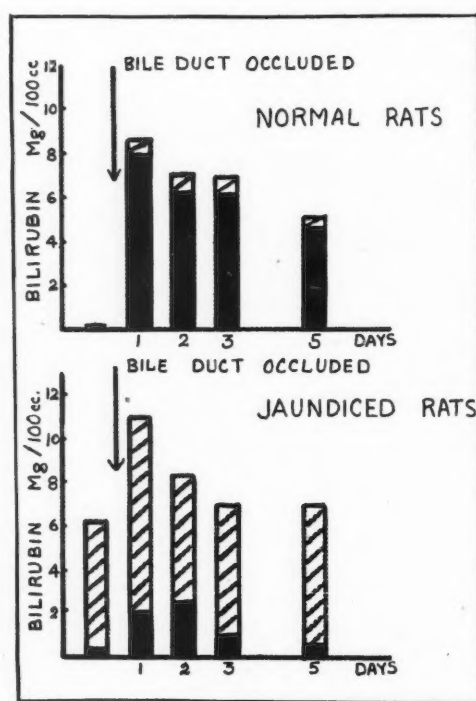


Chart 3

its inadequate formation by the liver of the jaundiced rat may be the cause of bilirubin retention in these animals.

Bile duct occlusion.—The experiment shown in Chart 3 was designed as a further test of the ability of the jaundiced rats to make direct bilirubin. By tying the bile ducts a true obstructive jaundice was produced in normal and in jaundiced rats. In the normal rats the picture is one of classical obstructive jaundice in which the accumulation of direct bilirubin predominates

over indirect bilirubin. In the jaundiced rats much less direct bilirubin is formed and the blood bilirubin picture remains largely indirect in type. Some direct bilirubin is however formed, showing that the jaundiced rats are not entirely deficient in their ability to make direct bilirubin. These experiments thus provide supporting evidence for the cause of jaundice in the rats suggested by the results of the bilirubin injection experiment.

The experiments are of further interest in that they demonstrate the failure of the bilirubin reaction as an aid to clinical diagnosis in the special case of the jaundiced rats. Even when the bile duct is tied the serum bilirubin remains largely indirect in type.

Bile pigment excretion.—Investigation of existing methods for urobilinogen and urobilin has revealed that they are even more unreliable than has been previously considered, and for this reason the actual figures obtained have not been considered sufficiently accurate to report. Qualitatively, whether the stool urobilin was measured as urobilin or as urobilinogen, the results would indicate that less appears in the stool of the jaundiced rats than in the stool of the normal rats. It does not appear to be entirely absent in the stool of the jaundiced rats.

Liver function tests.—The abnormal findings in the bilirubin liver function test have already been reported. The plasma prothrombin level was normal in the jaundiced rats, both normal and jaundiced rats' plasma clotting in an average of 14 seconds when tested by the method of Quick.⁵ The Takata-Ara test was negative. Brom-sulphonphthalein excretion was normal, the injection of 5 mg. resulting in the retention of 5 to 10 per cent of the dye in 10 minutes and less than 2 per cent in 30 minutes in both normal and jaundiced rats.

SUMMARY

1. The problem of hereditary jaundice in the rat was investigated by searching for evidence of a possible hæmolytic process or of a possible impairment of bilirubin excretion.

2. Indirect evidence of a hæmolytic process was the fact that the bilirubin in the serum is invariably indirect in type. From the blood picture, red-cell fragility determinations, and post-mortem examinations no direct evidence of a hæmolytic process sufficient to explain the jaundice was obtained. An unexplained slight

anæmia is usually present which is not directly related to the amount of bilirubin in the serum. The fragility of the red cells in hypo- and hypertonic saline is normal, and in saponin the red cells show increased resistance. The serum of jaundiced rats was more protective towards saponin hæmolysis than normal rats' serum. No evidence of marked bone-marrow or splenic hyperactivity was found. The spleen is smaller than normal.

3. Intravenous injection of bilirubin revealed a marked impairment of bilirubin excretion. In experimental bilirubin retention in normal rats, direct bilirubin was formed from the injected bilirubin. This did not occur in hepatectomized rats nor in the jaundiced rats.

4. Tying the bile ducts of the jaundiced rats further revealed the abnormality in direct bilirubin formation. The serum bilirubin remained largely indirect in type in spite of the imposed acute obstruction.

5. Urobilin excretion in the stool was less than normal but not entirely absent.

6. Brom-sulphonphthalein and Takata-Ara liver function tests were normal. Plasma prothrombin was normal.

7. It is concluded that the jaundiced rats have a retention jaundice which the evidence would suggest is caused by an inability of the liver to make direct bilirubin at a rate sufficient for normal excretion.

8. Attention is directed to the failure of the bilirubin reaction as an aid to clinical diagnosis in the special case of the jaundiced rats.

9. It is suggested that the jaundiced rats present a close resemblance to the cases of familial jaundice in human beings found by Damashek.⁸

The expenses of the investigation were defrayed by a grant from the Banting Research Foundation, Toronto, and the work was performed under the direction of Dr. J. C. Meakins, Director of the Department of Medicine and the University Clinic, to whom our grateful thanks are due.

For his kindness in generously supplying the jaundiced rats our thanks are due to Dr. J. W. MacArthur, Department of Genetics, University of Toronto.

REFERENCES

1. GUNN, C. K.: *J. Heredity*, 1938, 29: 137.
2. HIGGINS, G. M. AND STASNEY, J.: *Folia Hæmatol.*, 1937, 56: 189.
3. MURRAY, E. D. G.: *Med. Res. Coun. (Spec. Report Ser.)*, 1929.
4. GUNN, C. K.: Personal communication.
5. QUICK, A. J.: *Am. J. Physiol.*, 1936, 114: 282.
6. EVELYN, K. A.: *J. Biol. Chem.*, 1936, 115: 63.
7. MALLOY, H. T. AND EVELYN, K. A.: *J. Biol. Chem.*, 1937, 119: 481.
8. Personal communication.

THE LAUGHLEN TEST AND BLOOD DONORS*

By P. H. GREEY, M. M. BRACKEN AND MISS E. PAUL

Toronto

THE recent regulation passed by the Ontario Legislature,¹ that all professional blood donors registered on public hospital lists must be examined every six months by a serological test for the detection of syphilis, serves as an indication of the general interest that is being taken in the prevention of transfusion syphilis. It is well recognized that complete protection can not be given by tests made on professional donors every six months, or even every month, and, since the layman is not in a position to know the danger involved, hospitals should take every possible precaution to see that patients do not acquire syphilis from transfusion. It is highly desirable, therefore, that a serological test for syphilis be performed on all blood donors just prior to transfusion, irrespective of whether they are professional donors, relatives, or friends of the recipient.

The serological examination of all blood donors has been a routine procedure at the Toronto General Hospital for some time past. The purpose of this communication is to record the incidence of sero-positive reactions among these donors, together with observations on the merits of the serological reaction used.

Because the facilities of a transfusion service must be available at any hour of the day or night the serological reaction selected to detect syphilis in a donor must be one which can be rapidly performed and easily read. At this hospital the blood groups of the patient and prospective donors are determined by the interns attached to the various medical and surgical services. Red blood cell suspensions and sera from the patient and donors selected are sent to the department of bacteriology for cross-matching. This is carried out by the interns attached to the laboratory service who recheck the blood groupings and determine if the bloods are suitable by means of both the major and minor relationships. In order to detect syphilis we therefore required a quick and highly efficient reaction which could readily be set up and read by interns possessing comparatively little previous serological training.

The Laughlen test, with which we had had considerable experience, was finally selected as the one most likely to fulfil the above conditions.

Inactivation of serum for the Laughlen test.—The sera generally used in serological studies are not perfectly fresh, while blood from donors are usually examined almost immediately. Since it is possible that fresh sera might behave in the Laughlen test somewhat differently from sera which had stood for some time at room or refrigerator temperatures a necessary preliminary to the adoption of the test for transfusion purposes was a comparative study of the accuracy of the reaction, using fresh unheated serum, inactivated serum, and unheated stored serum. For this investigation the blood of sero-positive persons under treatment was centrifuged as soon after collection as possible, and a Laughlen* test was carried out with the fresh unheated serum. A second test was done after inactivation of the serum at 56° C. for 30 minutes. The remainder of the specimen was stored in the refrigerator as whole clotted blood, and several days later the serum, unheated, was again tested by the Laughlen reaction. Separate specimens of blood from each case were studied independently by both the Kahn and Wassermann tests. The results of the Laughlen test, using fresh unheated serum, unheated serum stored for several days, and inactivated serum were then correlated with those of the Kahn and Wassermann reactions. While only 40 sera positive by both Kahn and Wassermann reactions were examined in this way, 4 (i.e., 10 per cent) gave negative Laughlen reactions when fresh unheated serum was used. All of these false negative reactions were positive, however, when the same serum, inactivated or stored for several days but unheated, was used for the Laughlen test. These experiments done in 1935 were not published.

Laughlen² in describing his test at first believed that accurate results could be obtained using unheated serum, but inactivation was advised in 1938 following a study of 1,834 blood

* From the Department of Bacteriology of the Toronto General Hospital.

* The reagent was kindly supplied by Dr. G. F. Laughlen as it was not commercially available at that time.

samples tested before and after heat inactivation.³ Of this number 1,777 gave negative results with both unheated and heated serum. But of 56 positive with inactivated serum 4 gave negative and 5 doubtful reactions with the corresponding unheated serum. In other words, 4, or possibly 9, sero-positive cases would have been missed through the use of unheated serum. While it may be possible to obtain a high percentage of accurate results without the necessity of heat inactivation of the sera (calculated on the basis of the total number of specimens tested) a not inconsiderable percentage of false negative reactions are obtained when only the sero-positive cases are considered. Unheated serum therefore fails in the very cases that must be detected. We are convinced of the absolute necessity of inactivating the serum prior to use in the Laughlen reaction for the exclusion of syphilis in blood donors.

Routine method.—The main procedures of the routine method which we adopted for the detection of syphilis in blood donors may be briefly outlined as follows: (1) 0.5 c.c. of the donor's blood serum is transferred to a Kahn tube and is inactivated at 56° C. for half an hour. A drop is then placed on a clean slide by means of a capillary pipette, and to this a slightly smaller drop of reagent (Lederle) is added. (2) The reagent and serum are mixed by tilting the slide back and forth. If after 10 minutes of observation no change has been observed the test is considered negative. (3) Blood from all donors is sent to the serology department where an overnight Kahn test is done. If the latter gives a positive result the serum is further studied by means of the Wassermann reaction. (4) Should the Laughlen reaction be positive the donor is reported as not suitable for use, but the hospital superintendent is not notified unless positive Kahn and Wassermann reactions are obtained.

RESULTS AND COMMENTS

In connection with our transfusion service 2,200 persons who offered themselves as donors have been tested by both the Kahn and Laughlen reactions. Fifteen of these were sero-positive by the Laughlen test, but only 8 of the 15 gave positive results with the Kahn and Wassermann reactions, and only these 8 were listed as syphilitics. Thus in this series about half of the positive Laughlen reactions were false positives. On the other hand, in fairness to the test, it should be noted that this corresponds to only

0.32 per cent false positives in the total series. And, further, in no instance among these 2,200 bloods was the Laughlen test negative when the Kahn reaction was positive. From the point of view of transfusion the test errs on the safe side, but from these results it would seem that a serological diagnosis of syphilis should not be made on the Laughlen test alone. We believe that for diagnostic purposes a positive Laughlen result must be checked by reactions possessing greater specificity.

In this series 6 of the 8 sero-positives encountered were not professional donors but either relatives or friends of the patients. The duty of hospitals to prevent the possible transfer of syphilis from this type of donor should be emphasized.

The Laughlen test has proved to be a valuable rapid reaction for helping to eliminate the possibility of syphilis in prospective blood donors. While some experience is necessary the reaction is comparatively simple to perform and read. We have found it entirely suitable as an exclusion test, for use by a changing personnel.

In this consecutive series of 2,200 prospective blood donors 0.36 per cent were positive by the Kahn and Wassermann tests. This compares with 1.5 per cent in our public ward admissions. In New York City, Goodman,⁴ using the Wassermann reaction, found among applicants seeking to become professional blood donors an incidence of sero-positives of 0.68 per cent for white people and of 25 per cent for negroes. On the other hand, relatively high incidences of sero-positives have been reported from blood banks, such as Philadelphia,⁵ 4.7 per cent, and Chicago,⁶ "not over 10 per cent".

CONCLUSIONS

1. An exclusion test for syphilis should be performed on all blood donors prior to transfusion.
2. The Laughlen test is a satisfactory method for the detection of syphilis in blood donors, provided the serum is inactivated before use.
3. In this series of 2,200 tests no serum was found that was negative by the Laughlen and positive by the Kahn test.
4. Of 2,200 prospective blood donors 0.36 per cent were sero-positive by the Kahn and Wassermann reactions.
5. In this series, out of 15 sera positive by the Laughlen test only 8 gave positive Kahn and Wassermann reactions.

6. For diagnostic purposes a positive Laughlen reaction should always be checked by methods possessing greater specificity, otherwise individuals may be erroneously thought to have syphilis.

REFERENCES

1. Regulations under Public Hospitals Act, Department of Health of Ontario, 1938, p. 10.
2. LAUGHLEN, G. F.: A rapid test for syphilis, *Canad. M. Ass. J.*, 1935, 33: 179.
3. *Idem*: The Laughlen test for syphilis, *Canad. Pub. Health J.*, 1938, 29: 396.
4. GOODMAN, H.: In discussion of article on control and prevention of transfusion syphilis, Rein, C. R., Wise, F. and Cukerbaum, A. R.: *J. Am. M. Ass.*, 1938, 110: 18.
5. CAMERON, C. S. AND FERGUSON, L. K.: The organization and technique of the blood bank at the Philadelphia General Hospital, *Surgery*, 1939, 5: 237.
6. FANTUS, B. AND SCHIRMER, E. H.: Blood preservation technique, *J. Am. M. Ass.*, 1938, 111: 317.

RHEUMATIC HEART DISEASE IN ADOLESCENCE*

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Montreal

IN accepting your Committee's request that I address you I realize the fact that when one has an opportunity to study any particular phase of a subject it does convey certain responsibilities to one's fellow practitioners—that they should be made aware of the knowledge gained through such opportunity, and it is in response to such responsibility that I dare present to you, many of whom have had much longer experience than I, a communication on such a subject as "Rheumatic heart disease in adolescence". My own interest has been in the general picture of rheumatism in childhood, rather than in the effect of the disease on the cardiac mechanism, particularly with regard to determining when rheumatic infection is no longer active.¹ If during the course of my remarks I make statements which do not seem to be substantiated by facts, but are rather clinical impressions, I hope that you will bear with me.

Rheumatic heart disease is, unfortunately, one of the commoner ailments of the older school age group—of 10 to 16 years. It is unquestionably one of the most crippling of all diseases and the greatest single cause of death among adults. I wish to stress this point, for you must appreciate that any attack of rheumatic infection is not an isolated incident in a person's life, but one of a long and progressively damaging series of events going on from childhood, through adolescence, to adult life. What factors determine whether he will acquire heart disease with his first attack of activity at

five, or his third at eighteen, or completely escape, we know not. There are apparently two periods in childhood when rheumatic heart disease is more common; the first rise in the chart of frequency occurs from five to seven years, and a second more precipitous rise at nine or ten years. Unfortunately such charts are elaborated after, rather than before, the fact; that is, we establish such figures by going back over the history of patients. The point I would make is the fact, stressed by many of the older writers, that rheumatic heart disease occasionally has an early and most insidious onset, with no frank symptoms or signs, no acute arthritis or stiff neck or knees, only a history of being unwell with low-grade fever and occasional precordial pain, a state that has been aptly described as "the unwell child"—poor appetite, loss of colour, failure to gain in weight, ready fatigue on moderate exertion, loss of energy; that is, the signs of some type of low-grade infection or intoxication, the cause of which can only be found by most careful examination. One might almost say that any school child who fits the category of the unwell child must be considered a rheumatic subject until other cause is found for his lack of health.

The commonest clinical sign of rheumatic heart disease is, of course, the appearance of a low-pitched systolic murmur at the apex of the heart, associated frequently with a clinically recognizable degree of enlargement of the relative cardiac dullness, occurring usually during or following a febrile illness. The febrile illness may be an acute upper respiratory infection, acute tonsillitis, scarlet fever, pneumonia, influenza or frank rheumatic arthritis. This is the accepted view. It does, however, require the qualification that such changes occur after

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many febrile illnesses in childhood, and are not of themselves an indication of heart disease; but it is the course which they pursue which determines their nature. We are all familiar with the faint apical systolic murmur which occurs in a child convalescent from pneumonia, which disappears after a few days of observation and which we put down to a "toxic myocarditis" and suggest that it is due to a slight cardiac dilatation with some incompetence of the mitral ring. I know of no way of distinguishing what may be the earliest clinical evidence of rheumatic heart disease from one of these mild post-febrile evanescent murmurs, except by careful and repeated observation and

a search for other evidence of rheumatic infection.

Even in known rheumatic persons the recognition of such apical systolic bruits does not of itself definitely prove the presence of heart disease, though the likelihood is admittedly great. During the past five years, of 121 adolescent children admitted to our Rheumatism Service at the Children's Memorial Hospital, Montreal, 10 between the ages of 10 and 15 years showed such fleeting apical murmurs during the course of their illness and later had no demonstrable heart disease. However, 35 others of the same group with the same early signs did later have other evidence of

FREQUENCY OF MANIFESTATIONS OF RHEUMATIC INFECTION

MALES

Male	Age of		First S. & S.	Other manifestations					X-ray Enl.	A.V. Cond.	Epis. Att.	Nod.	Foci
	Onset	Adm.		M. In.	M. St.	A. In.	A.R.F.	Ch.					
1	11	11	A.R.F.	x	x	x			x	.2	4		
2	12	12	A.R.F.	x								x	Teeth T. & A.
3	6	15	A.R.F.	x	x	x			x	.2			
4	4	14	Chorea	x	x	x	x		x			x	Teeth T. & A.
5	11	14	A.R.F.	x	x	x			x	Normal to .24		x	
6	9	12	A.R.F.	x					x				
7	7	10	A.R.F.	x					x				Teeth T. & A.
8	9	10	Card.	x	x	x	x		x	.22-.2		x	T. & A.
9	8	14	Card.	x	x				x		9	x	Sinus Tonsils
10	8	10	A. Tons.	x	x		x		x	.2	11		
11	10	10	A.R.F.	x									
12	5	10	A.R.F.	x	x				x		2	x	
13	10	13	A. Tons.	x	x	x	x		x	.18			
14	7	10	A.R.F.	x									
15	10	10	A.R.F.	x					x	.22-.28		x	
16	12	12	A.R.F.	x	x	x		x	x			x	
17	13	13	Card.	x			x						
18	7	13	A.R.F.	x	x	x		x	x	.2			T. & A.
19	10	11	A.R.F.	x	x				x				

Chart 1

First S. & S.—First signs and symptoms. M.In.—Mitral insufficiency. M.St.—Mitral stenosis. A.In.—Aortic insufficiency. A.R.F.—Acute rheumatic fever. Ch.—Chorea. X-ray Enl.—Enlargement of the heart by x-ray. A.V. Cond.—Auriculo-ventricular conduction time. Epis. Att.—Epistaxis attacks. Nod.—Nodules. Foci.—Foci of infection.

FREQUENCY OF MANIFESTATIONS OF RHEUMATIC INFECTION

FEMALES

Female	Age of		First S. & S.	Other manifestations					X-ray Enl.	A.V. Cond.	Epis. Att.	Nod.	Foci
	Onset	Adm.		M. In.	M. St.	A. In.	A.R.F.	Ch.					
1	6	11	Chorea	x	x		x		x	.16-.2 -.24			
2	7	10	A.R.F.	x	x	x			x		4		Teeth T. & A.
3	10	10	A.R.F.	x	x	x			x				T. & A.
4	11	11	A.R.F.	x						.2			T. & A.
5	10	11	Chorea	x			x						
6	4	10	Chorea	x	x				x				T. & A.
7	10	11	Chorea	x	x	x			x				T. & A.
8	7	11	A.R.F.	x	x				x		6		
9	8	11	A.R.F.	x	x				x	.24-.32	5	x	T. & A.
10	10	10	A.R.F.	x					x				T. & A.
11	10	12	A.R.F.	x	x			x	x	.2			
12	11	12	A.R.F.	x	x				x			x	
13	12	12	A.R.F.	x				x		.18-.12		x	Te. & A.
14	5	10	A.R.F.	x	x	x							
15	9	10	A.R.F.	x	x				x				Teeth
16	10	10	A.R.F.	x					x		4		

Chart 2

First S. & S.—First signs and symptoms. M.In.—Mitral insufficiency. M.St.—Mitral stenosis. A.In.—Aortic insufficiency. A.R.F.—Acute rheumatic fever. Ch.—Chorea. X-ray Enl.—Enlargement of the heart by x-ray. A.V. Cond.—Auriculo-ventricular conduction time. Epis. Att.—Epistaxis attacks. Nod.—Nodules. Foci.—Foci of infection.

SUMMARY OF 35 CASES

Adolescent carditis—35 cases—19 males, 16 females.
Age 10 to 15 years inclusive—1935-1938 inclusive.
Total cases treated..... 121
Percentage carditis..... 29

CARDITIS

Average age of onset..... 8.83 years
Average age of admission..... 11.3 years

First clinical manifestation:

Acute tonsillitis..... 2 cases
Acute rheumatic fever..... 25 cases
Rheumatic heart disease..... 3 cases
Chorea..... 5 cases

Type of carditis:

Mitral insufficiency..... 12 cases
Mitral insufficiency and stenosis.. 11 cases
Mitral insufficiency and stenosis,
and aortic insufficiency..... 12 cases
Carditis with enlargement by x-ray... 27 cases
Mortality..... 2 deaths

(1) Sub-acute bacterial endocarditis.

(2) Fulminating mitral insufficiency, stenosis
and aortitis, with acute dilatation. Died
within 24 hours of admission.

The striking feature in all of the charts is the frequency with which acute rheumatic fever appears in the history of all these patients.

Chart 3

heart disease. I know of no way to distinguish them, as I say, except by repeated and close observation.

Of these 35 cases, 16 were girls, and 19 were boys. The accompanying charts show the details of interest concerning this group.

In summary, the average age of onset of the cardiac disease was 8.83 years, and the average age of admission to the ward was 11.3 years. The first clinical manifestations of rheumatism were acute rheumatic fever in 25 cases, chorea in 5, rheumatic heart disease in 3 and acute tonsillitis in 2. The type of carditis as determined clinically was mitral insufficiency in 12 cases, associated with stenosis in 11 other cases, and with aortic disease in another 12 cases. Enlargement of the heart was shown by x-ray examination to be present in 27 of the 35 children. Two patients died while under observation, one from acute bacterial endocarditis, and one from acute dilatation with

mitral insufficiency, stenosis and aortitis, who died within 24 hours of admission to the hospital.

While admittedly the electrocardiogram is not a necessary adjunct to the diagnosis and care of rheumatic heart disease, the changes in the speed of conduction of impulses through the heart which can be shown by this means are of interest and frequently of diagnostic value. Observe a normal electrocardiographic tracing and the P.R. interval or conduction time is shown for a child to be well within the normal limits, 16/100 seconds. If later in the presence of a faint apical bruit one can show that such conduction time has increased to 20 or 22 hundredth seconds, the implication of rheumatic heart disease is made the greater. John Keith² has suggested that there is a distinct relationship between the increased conduction time and the murmur, in that the latter may be due to inefficient and irregular ventricular systoles caused by the delayed conduction of impulses to the ventricular musculature and unequal closure of the leaflets of the mitral valve. Suffice it to say, that evidence of a delayed electrocardiographic conduction time in the absence of recent influenza and typhoid fever may be considered evidence of rheumatic heart disease. Changes in the size of the cardiac shadow, which can be demonstrated to occur by x-ray, are of value in conjunction with other physical signs of heart disease, and are of course more trustworthy than manual percussion. However, repeated careful physical examination, possibly over many months, may be necessary before a positive diagnosis can be made.

It is recognized that rheumatic heart disease may occur in the absence of acute arthritis. However, I doubt that it occurs with as great frequency as the textbook authors would have us believe. An accurate and patiently taken history will usually reveal some minor and forgotten fleeting arthritis. While on this point, I would mention that few so-called "growing pains" are rheumatic; many are due to foot strain and faulty posture, and many more are probably truly related to the physiological process of growth and are of unknown origin. The great majority of children who complain of leg pains are not suffering from rheumatic fever.^{3, 4} However, in relation to chorea as a precursor of heart disease, Usher has shown that rarely, if ever, does "pure chorea precede

heart disease", but that a carefully taken history will usually reveal a story of some arthritic pain of greater or lesser severity. Thus in those children suffering from chorea who develop heart disease it may be doubted that rheumatic heart disease occurs very often without some preceding arthritis of major or minor degree.

The treatment of rheumatism and rheumatic heart disease offers many difficulties. If one takes as a guide the accepted therapy of tuberculosis, and goes on from this generalization to particularize, one is probably on safe ground; rest in bed, good food, fresh air and tonics, and above all, more rest; in this one has almost covered the field of general treatment, in that admittedly we have no specific therapy to offer to our patients. The great difficulty is in determining when the point has been reached that the disease is no longer active and one may safely allow patients to be up and about, and remove their obvious foci of infection, if we think they should be removed. On this point may I be brief and specific, and I am no doubt open to correction and contradiction. I do not regard rheumatic disease, past or present, as necessarily an indication for the removal of tonsils or teeth or draining of sinuses. The interference with such foci must be determined on the same grounds as in the non-rheumatic person, with the same care and exercise of clinical judgment; with this proviso, that if possible no operative interference should be practised on the rheumatic child until all evidences of activity of his disease have subsided. We do know that reactivity of rheumatic disease may follow removal of teeth or tonsils in any rheumatic child, and any operation should be undertaken with extreme caution. Finally, I do not believe that any child who has had rheumatic heart disease of a severity to produce cardiac failure or decompensation should ever be subjected to a tonsillectomy unless the evidence of direct association between the two, the throat infection and the heart disease, is beyond doubt.

It is important that we recognize the chronicity of rheumatic fever in childhood, and that the signs and symptoms may continue almost indefinitely. Laboratory studies present evidence of active rheumatic fever long after the clinical evidence of the disease has subsided, and so long as there is even laboratory evidence

of activity, primary or continued heart damage is possible. This phase of rheumatic fever has been studied by many workers. Our own studies tend to show that the sedimentation rate is probably the most delicate test for activity of rheumatic fever in that it is the last abnormality to return to normal after activity.⁵

From the practitioner's point of view I would stress three observations which may be used in the home in the determination of cessation of activity of rheumatism.

1. *The body weight.*—While it is admitted that patients at rest in bed may gain weight in the presence of both progressive rheumatism and tuberculosis this is uncommon. So the presence of a steadily rising weight curve may be used as evidence of cessation of activity.

2. *A normal sleeping pulse-rate.*—The alert pulse in childhood is too readily affected by emotion to be of value in determining the activity of rheumatic heart disease. However, the presence of a gradually falling sleeping pulse-rate is of definite value in the determination of cessation of activity. Thus a sleeping pulse-rate falling gradually over a period of weeks from 96 to 66, and such relative bradycardia is frequent, is to be interpreted as an evidence of cessation of activity. Conversely, the presence of a sleeping pulse-rate of 90 or over in an adolescent who has had signs of arthritis should be considered evidence of rheumatic carditis that is active; and

3. *The sedimentation rate, i.e.,* the rate at which the red cells fall through uncoagulated plasma should be a well established, measurable figure. Alteration of this rate is considered evidence of some abnormal process going on in the body, which alters the albumin globulin ratio in the blood, and infection is known to be one of those abnormal processes; hence the alteration of the sedimentation rate may be taken as an evidence of activity of rheumatic heart disease, though it applies equally to the determination of the activity of tuberculosis, and is in no way specific. However, one may make a clinical estimation of the activity or inactivity of the disease by means of these observations which I commend to your use—the body weight, the sleeping pulse and the sedimentation rate. Rest in bed is essential until all these observations have been normal for a minimum period of one month.

During the period of prolonged bed rest, besides the offering of a good and adequate diet, the maintenance of school instruction if possible, and the education of the patient and his family concerning the disease, two things are of major importance, first, the avoidance of upper respiratory infections, the common cold, as these directly affect the prognosis of the individual case as we shall see, and, secondly, freedom from emotional and family difficulties. The greater the number of "free" individuals of his own age-group with whom the child comes in contact, the greater the danger of infection. From this point of view such patients do better in an institution than in a crowded and emotional household, particularly if the institution be prepared to offer adequate supervision and occupational and recreational therapy, and where satisfactory discipline and rest may be obtained. The lack of parental discipline among children in their homes is one of the strongest arguments in favour of hospitalization of children with rheumatic heart disease. Finally, regarding prognosis, one may dare to say that the older the child is in years before he acquires rheumatic disease, the less likely he is to develop heart disease. That is, the youth of 16, having his first attack of rheumatic fever, is very much less likely to develop heart disease than his brother of 6 years, living in the same household, who is almost certain to be a cardiac cripple in early adult life. Secondly, that the longer a person who has had rheumatic disease lives without recurrence, the less likely is the recurrence to appear, so that after six years of freedom from signs of active rheumatic disease he is probably safe. Thirdly, that the most frequent single preceding circumstance associated with the reactivation of rheumatism is the common cold. Unquestionably the rheumatic person who acquires an upper respiratory infection should go to bed and stay there until his signs of active infection have completely disappeared.

I refrain from commenting on the particular prognostic importance of the various individual cardiac manifestations. I do not know what the significance of a soft diastolic aortic murmur is in a child, in relation to probable livelihood, though the peripheral evidence of aortic incompetence may not appear for months or years, and I am anxious only that you should

appreciate that it means active rheumatic heart disease, as does a mitral mid-diastolic murmur, which may be fleeting in character and not signify early mitral stenosis, or the presence of a third heart sound of unknown origin and significance. We should not forget that the patient has active rheumatism in listening to his heart murmurs. Rheumatic nodules occur frequently during rheumatic activity, sometimes when the activity is subsiding, and, in our experience, are usually associated with the presence of heart disease. Erythema multiforme and marginatum and epistaxis also occur with active rheumatic disease, and are of particularly evil prognostic importance in our limited experience.

The best long-term study of rheumatic disease with which I am familiar is that reported by Jones, of Boston.⁶ He followed 1,000 rheumatic fever patients for a ten-year period. Of these 672 had heart disease when first discharged from hospital, 71 more later developed heart disease, and half of these without later evident rheumatic fever. Of the 672, 230 died of their disease; in 188 the heart disease remained unchanged, in 120 it had progressed and in 119 had improved, and in one-half of these evidence of heart disease had disappeared. The mortality of the thousand is 24 per cent in ten years' time; the average age at death was 13 years, and of these 68 per cent

died during the first 6 years of their disease. Truly rheumatic heart disease is a disease of childhood with its highest mortality in adolescence. However, of Jones' thousand patients 60 per cent are living and have no indication of activity ten years after the onset of their rheumatic fever. "Despite the high mortality the finding of normal physical life in 60 per cent of such a large group at the end of ten years is heartening, and warrants continued attempts to see that patients have the best possible medical observation and care" (Jones).

In conclusion, I would ask your indulgence that I have seemed to wander so far from the rather restricted title offered me by your Program Committee. However, this I have done intentionally in the desire to stimulate your interest in rheumatic disease as a whole, rather than that you should view it only as it is manifested by the various changes produced in the cardiac mechanism, which we can recognize by clinical methods. Rheumatic heart disease is not a complication of rheumatic fever, but is part of the disease, and the cardiac manifestations must be studied from this point of view.

REFERENCES

1. STRUTHERS, R. R. AND BACAL, H. L.: *Canad. M. Ass. J.*, 1933, 29: 470.
2. KEITH, J.: *Arch. Dis. Child.*, 1937, 12: 70.
3. SHAPIRO, M. J.: *J. Ped.*, 1939, 14: 401.
4. HAWKSLEY, J. C.: *Brit. M. J.*, 1939, 1: 147.
5. STRUTHERS, R. R. AND BACAL, H. L.: *Canad. M. Ass. J.*, 1936, 35: 258.
6. JONES, T. D.: *J. Ped.*, 1939, 14: 410.

THE CARE OF THE PREMATURE CHILD*

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THE "care of the premature infant" is an old and oft repeated subject, but when one stops to consider that prematurity is the commonest cause of death during the first few weeks of life, and also accounts for more than 25 per cent of the total infant mortality rate, repetition can surely do no harm. For practical clinical purposes, we should class as a premature child, any infant, whether a single or multiple birth, born prematurely, at term, or even past term, whose body weight is less than 5 pounds.

Prophylaxis.—The prevention of prematurity is obviously a problem for the obstetrician, and since the cause of premature deliveries remains

obscure in 40 to 50 per cent of cases his hands are literally tied so far as this group is concerned; and other causes, such as placenta prævia and maternal traumatism, cannot be avoided, but with the remaining cases something can and is being done to lower the incidence. The prevention of maternal malnutrition (and by "malnutrition" I do not mean starvation, but a diet sadly lacking in vitamins, minerals and proteins); the diagnosis and treatment of syphilis in the early months of pregnancy; the newer therapeutic measures to combat the "habitual abortant" and the closer check on impending toxæmias of pregnancy and eclampsia are lessening premature births to a considerable degree; and the obstetrician

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is to be congratulated for his efforts along these lines.

The immediate care.—This is of paramount importance. The loss of body heat during delivery should be minimized; it may be the means to success. This is best accomplished by wrapping the infant in a heated, sterile blanket immediately he is delivered, and keeping him there while waiting the desired time to elapse before cutting the cord. During this period the head should be kept in a dependent position, to allow any mucus and secretions to escape from the respiratory passages; catheter suction can be carried out if necessary. Some obstetricians immerse the infant, all but the head, in a warm sterile bath (100 to 105°) until the cord is tied. When this procedure is completed he should be immediately placed in the heated bed, basket or incubator.

The maintenance of body temperature.—Due to the undeveloped state of the nervous system the heat-regulating centre is not properly functioning. When a normal infant is chilled he cries, squirms, vasoconstriction occurs, and his body temperature is prevented from dropping rapidly. Also the reverse; when extra heat is present vasodilation with sweating results, and a sudden rise in temperature is prevented. Not so with the premature infant. In the first place he is too feeble to cry and squirm. Vasoconstriction is practically absent and vasodilation, with sweating, occurs but little or not at all. So the premature child's temperature is regulated or governed by the temperature of his surroundings. In addition, the relative surface area of the body of a premature infant, being larger than in the normal baby, and the absence of subcutaneous fat also play a part in hindering self-temperature control.

The method of supplying and regulating external heat and humidity naturally varies with the environmental conditions under which the physician is working; it may be a hospital, a city home with adequate conveniences, or a humble rural dwelling. And here may I refer briefly to the work of Blackfan and Yaglou,¹ of the Harvard Medical School. They report results from over 7 years' work with premature infants in the "Conditioned Nurseries" where temperature, ventilation and humidity were accurately controlled from a central plant. They divided their premature infants into 3 groups: (a) those in the conditioned nursery

with high humidity; (b) those in the conditioned nursery with low humidity; (c) those in the unconditioned nursery where physical factors were allowed to fluctuate. Their results were noteworthy. In the conditioned nursery with high humidity the initial loss of weight was less, the gain in weight and length was more rapid, and the incidence of disturbances of digestion and of parenteral infections was less than in the conditioned nursery with low humidity and in the unconditioned nursery. Their conclusions were, roughly, that (1) The humidity best suited for stabilizing the body temperature of premature infants and helping their general progress appears to be about 65 per cent, with the temperature of the room ranging from 75 degrees with the larger to 90 or 95 degrees with the very small, feeble infants; (2) the lower the humidity, the higher the room temperature necessary; (3) a humidity of 30 per cent or less induces instability of body temperature with untoward effects, often leading to serious consequences.

The use of the conditioned nursery is naturally limited to a few large institutions. Likewise, the electrically controlled closed incubator, being quite expensive, is limited to a certain number of hospitals, and so the open heated bed and makeshift basket are the methods open to the majority of us, with extra heat applied by means of electric light bulbs, electric pads, or hot water bottles (160 to 180°). And these latter two methods prove quite satisfactory, even in the home.

In our centre we are getting away from the electric incubator, and having generally good success with the open heated bed. It consists of an ordinary deep cot. One sheet drapes over one side of the cot, both inside and out, passes under the mattress and up to drape the other side, again both inside and out. Similarly another sheet covers the inside and outside of both ends, being continuous under the mattress. The sides of these sheets overlap slightly at the corners of the cot and are pinned together.

A metal frame, about 5 inches high, made by the hospital engineer, fits on top of the crib. This has two cross bars, from one of which is suspended an electric light socket into which one, two or three bulbs may be inserted. From the other cross bar drapes a flap to protect the light from the infant's eyes. A third sheet is placed over the top of the frame and draped

about the outside of the crib. It is very economical, neat in appearance, provides lots of air space, and the temperature can be controlled quite easily, and certainly no draft is permissible.

The room set aside for the premature child should be one where room temperature can be adequately regulated and no draft ventilation obtained. A thermometer should be placed in the cot and, if possible, a hygrometer. Extra humidity can be supplied by the presence of shallow pans of water, a steam kettle, or if the room is steam-heated, the escape of steam permitted from the radiator. It takes a lot of moisture to get the humidity approximating 65 per cent, with very little danger of overstepping this mark.

Clothing is important in maintaining body temperature. We must remember that the heat must get to the infant, so the less clothing and covers he has, the warmer he will be. The very small and feeble are best wrapped in absorbent cotton, the face only exposed, for a temporary period. With the majority, in a bed such as I have shown, a gown of light flannel, fairly close fitting, a binder, and a diaper loosely folded into position, without any head covering, are all that are necessary. A light flannel blanket is adequate covering.

Early bathing or oiling is to be condemned.

The plan introduced by Sanford² in allowing the vernix caseosa to remain on the body is now becoming most popular, and so the oil rubs are best postponed for at least four or five or even seven days. These rubs then should be carried out in the bed, as should also the changing of diapers, feedings and other routine measures.

The respiratory activity of prematurely born infants is very poor. Severe asphyctic or rather apnoeic attacks are very frequent, alarming, and are the end-picture in a large percentage of fatal cases. Suggested causes of these attacks are: lack of coordination of the various respiratory centres in the brain; peripheral fatigue of the various respiratory muscles; the high hæmoglobin content of the blood stream. This last suggestion is based by Ylppo³ on the fact that the respiratory disturbances in prematurely born rabbits can be relieved by a generous venesection, and in adult rabbits a previously regular respiration can be made irregular and even periodic by the injection of erythrocytes. This complication is

best combated by the inhalation of oxygen or oxygen- Co_2 mixture, with artificial respiration, which must be conducted very cautiously to prevent traumatism. The injection of stimulants, such as coramine, lobeline, etc., has some beneficial effect. Ylppo advises the introduction of oxygen directly into the stomach, slowly and in small bubbles. He observed from autopsies on premature children that the gastric mucosa is especially rich in capillary loops, and we know that in certain fish the oxygen can be supplied by intestinal respiration, *i.e.*, the air swallowed by the fish comes out from the anus with a lower oxygen and higher Co_2 content. He recommends this procedure over the oxygen inhalation, reporting very gratifying results. It may be worth a trial.

Just as important as the regulation of temperature, humidity, etc., is the exclusion from the room of all unnecessary human beings, even if the feelings of well wishing relatives and friends have to receive a temporary jolt. The premature infant is very susceptible to respiratory infections, even more so than he is to nutritional disturbances. The wearing of gown and mask is absolutely essential by the attending nurse or parent who should be free from respiratory infection of any kind. All utensils, clothing, etc., should be scrupulously clean. Routine cleansing of the child's eyes, nose and mouth is not only unnecessary, but likely to prove harmful, and should be omitted.

During the first 12 hours no food or water is necessary. During the next 12 hours 4 feedings of boiled water and 2 feedings of milk may be given, varying in amount from 1 to 3 drams. Starting at the second day, regular feedings should be given day and night. For the majority, a three-hour feeding, 8 feedings in the 24 hours, is best suited. With the very small infants, where the gastric capacity is lessened, a greater number of smaller feedings may be necessary. These more frequent feedings present less difficulty when breast milk alone is used, since the emptying time of the stomach is much less with breast milk than with artificial formulæ. Extra fluids naturally must be administered. Plain boiled water, dextrose solution (2 to 5 per cent) or a half strength Ringer's solution may be used. One must strive to get a daily fluid intake of about $\frac{1}{8}$ of the body weight, increasing gradually to $\frac{1}{6}$ of the body weight.

The method of oral administration of food and fluids depends on the ability of the infant to suckle. The ordinary feeding bottle with a small nipple and the Brec feeder will suffice for many. The dropper will be necessary for the smaller and weaker, and if these fail gavage feeding will have to be instituted. The catheter is passed through the nose or mouth, a distance of approximately 4 inches, and about 5 minutes should be taken to feed by this method. If the feeding is run in too quickly vomiting is very likely to occur.

If difficulty is met in getting a sufficient intake orally we must resort to subcutaneous injections of glucose, of saline, or a combination of the two. A fact to bear in mind is that the scalp veins of the premature infant are usually quite prominent, and by using a Riehl stop-cock intravenous injections may be easily carried out. Where blood is needed for any reason this method will save resorting to the cut-down procedure.

Increases in food are based on the weight of the infant and his food tolerance. The smaller and more premature the infant, the more slowly the food is increased, but in this matter, the infants must be considered individually and no hard and fast rule can be laid down. However, we are now using a more concentrated feeding than was used, or even believed safe, a few years ago. One conclusion is unanimous when discussing the feeding of the premature, namely, that breast-milk is the feeding *par excellence*. Except during the first few days, when this milk may have to be diluted with boiled water, whole breast-milk is tolerated well, and in most cases it alone will suffice. However, in certain instances it is desirable to concentrate or fortify it by the addition of other foods. To increase the protein content, one part of skimmed, later whole lactic acid, milk may be added to three parts of breast milk. Some clinicians are combining two parts breast milk to one part evaporated milk, while others are adding dried foods such as lactogen or S.M.A., approximately one teaspoonful to each ounce of breast milk.

Where no breast milk is available, artificial feedings must, of necessity, be used, and many have been suggested, mostly all with reported good results. Among these might be mentioned, protein milk, concentrated, and with added carbohydrate, lactic acid milk, evaporated milk, S.M.A., lactogen, and a host of others. So again

it may be said that in dealing with the type of food, each patient must be considered individually. But here a word of warning. When using artificial feedings a much closer watch must be kept for any evidences of nutritional disturbances. They are far more likely to occur with these than when breast milk is used. As the infant increases in weight and age, a haphazard increase in the strength of the food must be guarded against. As stated previously we are using a more concentrated feeding now than before, and in many cases, as the infant takes a greater quantity, the strength of the mixture must be diluted instead of being increased, to safeguard against any nutritional disturbances.

The early addition of vitamins to the diet is of paramount importance. Orange juice should be started by the third week, starting with a quarter of a teaspoonful daily, and increasing gradually to approximately an ounce a day by the eighth week. Jaroschka,⁴ from his work, goes so far as to say that one of the causes of prematurity is the lack of vitamin C in the prospective mother's diet. He advocates vitamin C by mouth or injection even earlier than the third week. By the end of the third week cod liver oil must be started, as the premature infant is very prone to develop rickets. Starting with a few drops a day, it should be increased to one or two teaspoonfuls daily by the eighth week. If not tolerated well in the larger amounts, one of the concentrates, well fortified with vitamin D, may be used.

The development of secondary anaemia must also be safeguarded. Disintegration of blood corpuscles is more pronounced in premature children than those delivered at term. Also from autopsies it is learned that the iron content of the liver and spleen is relatively low in these infants. Therefore by the fourth week iron in the form of iron and ammonium citrate (1 grain per pound body weight daily) of "Ferro Chlor.", five to ten drops daily, should be given. Also raw egg yolk may be used, one egg yolk to each quart of milk. Liver injections and whole blood intramuscularly may be used in extreme cases.

Certain clinicians are advocating the use of hormones as an adjunct to the routine care of the premature infant. Schiller⁵ advocates the use of folliculin or oestrin, which he terms the proliferation hormone. (Progynon or theelin are commercial products.) He uses this sub-

cutaneously or intramuscularly, starting within the first 12 hours after birth. He gives 2 doses daily, from 20 to 50 international units per dose, and keeps this up for a period of 2 to 4 weeks. He claims his results were excellent in a large series of cases. Potter⁶ has been using œstrin in the form of progynon orally at the Bristol Maternity Hospital since September, 1936. She gives 500 international units in a drachm of warm water by mouth twice daily. She claims the initial loss of weight to be less, the gain more rapid, and that the infants feed much better when this is used.

Moncrieff⁷ administered thyroid gland to a series of premature infants. His object was not to make up any deficiency, but to supply a stimulant to hasten maturation, with its improvement in the essential functions, such as respiration, heat regulation, etc. One-twentieth grain of thyroid extract was given daily for each pound of body weight over a period of approximately two weeks. He reports that the infants on thyroid fed better and controlled their body temperatures better than those not receiving it.

Soldin⁸ advocates the injection of human serum, starting with 5 c.c. daily for 10 days; then 10 c.c. daily until the gain in weight is steady and satisfactory. He states the presence of its nourishment, hormones, vitamins and antibodies accounts for the beneficial results. The advantages of these therapeutic measures are still being argued, pro and con, in the different clinics.

In conclusion, may I leave this thought. A premature infant born without congenital disease or defect, if given proper care from the start, will most probably reach the average normal standard of development by the eighteenth month; with no lasting handicaps in life. By giving that extra care, we may bring forth a citizen much more useful than the odd nine or ten pounder.

REFERENCES

1. BLACKFAN, K. D. AND YAGLOU, C. P.: *Am. J. Dis. Child.*, 1933, 46: 1175.
2. SANFORD, H. N.: *J. Pediat.*, 1937, 11: 68.
3. YLPPO, A.: *Acta Pædiatrica*, 1935, 17: 122.
4. JAROSCHKA, K.: *Münch. Med. Woch.*, 1938, 85: 1871.
5. SCHILLER, W.: Lectures, Providence Hospital, Detroit, January, 1937.
6. POTTER, M. F.: *Brit. M. J.*, 1937, 1: 1201.
7. MONCRIEFF, A.: *Arch. Dis. Child.*, 1938, 13: 57.
8. SOLDIN, M.: *Fortschr. d. Therap.*, 1934, 10: 463.

THE EARLY INTRODUCTION OF SOLID FOODS IN THE INFANT DIET*

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THE age recommended at which solid foods should be added to the infant's diet varies widely with different pædiatricians. Brown and Tisdall, in "Common Procedures in the Practice of Pædiatrics", 1932, recommended the addition of cereal at 6 to 9 months in breast-fed infants, and as early as 5 or 6 months in those artificially fed. They started egg at 9 to 12 months and thick vegetable soup at 11 months. Griffith and Mitchell, in "The Diseases of Infants and Children", 1935, advised that cereals be started at 5 months, vegetables at 8 to 10 months. The feeding of egg was not mentioned under 1 year. Wright, in "Essentials of Infant Feeding and Pædiatric Practice", 1934, advised the addition of cereal and vegetables at 5 or 6 months, and egg at 9 to 12 months. Goldbloom, in "The Care of the Child", 1935, advocated starting

cereal at 6 months or before, and vegetables and egg at 6 months. Glazier,¹ in 1933, reported feeding strained vegetables and strained cereal by spoon as early as the second month. Caldwell,² in 1933, fed strained vegetables added to the milk feeding at the age of 6 weeks. Poole,³ in 1938, added strained vegetables to the formula as early as 2 weeks. Prior to the work now being reported it was the author's custom at the Infants' Home Clinic, Toronto, to start cereal at 4 to 6 months. About one-half to one month later vegetables were added, and egg was introduced at 6 to 9 months.

On account of this great diversity of opinion, I have during the past two and a half years observed the effects of the addition to the infant's diet, at the very early age of 1 month, of (1) egg; (2) pablum, and (3) vegetable.

Ninety-one infants placed in boarding homes composed the group. The majority were artificially fed from 2 weeks of age, and all artificially fed after 3 months. They were placed

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fairly consecutively in four groups. As will be seen from Table I the control and pabulum cases are more numerous than the others. This is due to the fact that after some experience with the solid feedings there was no hesitation in placing an infant on pabulum, even if there was a gastrointestinal upset with as many as four or five loose fluid stools per day. In fact, 6 of the 27

TABLE I.
NUMBER OF INFANTS IN THE DIFFERENT GROUPS UNDER
OBSERVATION AT 1, 2 AND 3 MONTHS OF AGE.

	1 month	2 months	3 months
Controls	29	29	22
Egg	17	13	12
Pabulum	27	26	19
Vegetables	18	18	11

pabulum cases were actually having disturbed stools at the time when the addition was made. Six of the 29 control cases had disturbed stools before the observation was started, though of less severity. Vegetables were not added if the baby was having loose stools at 1 month, although two infants had had loose stools 1 week previous to this addition. Considerable hesitation was felt soon after the observations were started about adding egg, unless the infant was having good stools. The length of stay in the boarding-home varied. It was impossible to foretell how long the child would remain with the clinic. This explains the drop in numbers at 5 months.

Group 1 consisted of 29 infants who were fed milk dilutions with no addition of solids.

Group 2 started with 17 infants. They had one-quarter sieved hard boiled egg yolk added to the day's feeding, and increased by one-quarter yolk every two days until receiving the whole yolk.

Group 3 started with 27 infants. One-half ounce, dry weight, of pabulum was added to the diet. This makes up in moist form about 6 rounded tablespoonfuls. It was started in a small amount and increased as quickly as possible, so that by 1½ to 2 months of age the baby was taking the full amount. In most cases at least part of the pabulum was fed by spoon from the first addition and by three months of age the whole amount was spoon-fed.

Group 4 consisted of 18 infants. They were fed single or mixed canned sieved vegetables, with the exception of spinach, no brand being specified. This was given undiluted by spoon, starting with a small amount and increased to

2 tablespoonfuls as the baby would take it. Usually the full amount was being given by 6 weeks of age.

In all children, no matter what the previous feeding, pabulum and vegetables were started at 5 months of age.

DIFFICULTIES

Four babies could not be established on egg. Two of these had diarrhoea and vomiting when egg was added, and in the other two the diarrhoea and vomiting were decidedly less each time the egg was removed. Three others had loose stools but egg was eventually continued. One infant dawdled over feedings after egg was added and two did not always finish the bottle. One child with loose stools was more contented when the egg was in the feeding.

One baby could not be established on pabulum, due to crossness, vomiting and varied stools. It was felt that the lack of success in this case was due to poor management on the part of the mother and foster mother rather than to the food itself. There were four infants with whom there was difficulty getting them to take the pabulum at first.

Three infants did not take the vegetables at all well at first, and two others took them well at first, but at 4 months, with a change of foster home, had difficulty for two weeks.

Stools.—In considering the effect of various solid foods upon the bowels it must be remembered that in the 27 cases placed on pabulum 6 gave a history of disturbed stools at the actual time the addition was first made; six of the 29 control cases at the same age had disturbed stools, though of less severity. The number of instances in which there were subsequent gastrointestinal disturbances, as evidenced by increase in frequency or change of consistency of the stools, was no greater in the group of infants receiving pabulum than in the control group. This held true from 1 month, the beginning of the period when solids were added, to the 11th or 12th month. In fact, in two breast-fed infants aged 1 month, having frequent loose stools in spite of protein milk mixture given before nursings, the stools became normal within 36 hours after protein milk was replaced by 1 tablespoonful of pabulum.

Out of the 17 infants originally placed on egg, 2 had slightly loose stools at the time of the addition of the egg. Out of the 17 four had to be permanently discarded from the observation

on account of diarrhœa and vomiting due to the egg. In 3 other infants fed egg minor periods of diarrhœa occurred, but not severe enough to necessitate permanent removal of egg from the diet.

On the whole, the infants placed on vegetables had less frequent and better digested stools at the time when the supplement was added than those infants placed in the other groups. None had to be removed from the observation on account of diarrhœa, and in general this group compared favourably with the control and pabulum groups.

The babies were weighed and their hæmoglobin estimated by the Evelyn photo-electric method, at 2 or 3 weeks, 1, 1½ and 2 months, and each month to 5 months of age. In Chart 1

the time at which the supplementary feedings were started, in all of the four groups the hæmoglobins were equal. From the second to the fifth month of age, there was a rise in the hæmoglobin in all groups, but there was not sufficient difference in the rate of increase of hæmoglobin in the different groups to be of any significance.

CLINICAL IMPRESSIONS

It was surprising how eagerly some infants, even at 1 month of age, took the first solid feeding—much to the delight of the foster mother. Spoon-feeding was established with less difficulty at 1 month of age than at 5 or 6 months. New solids were usually introduced with greater ease at 5 months when spoon-feeding had been started at 1 month. Most foster

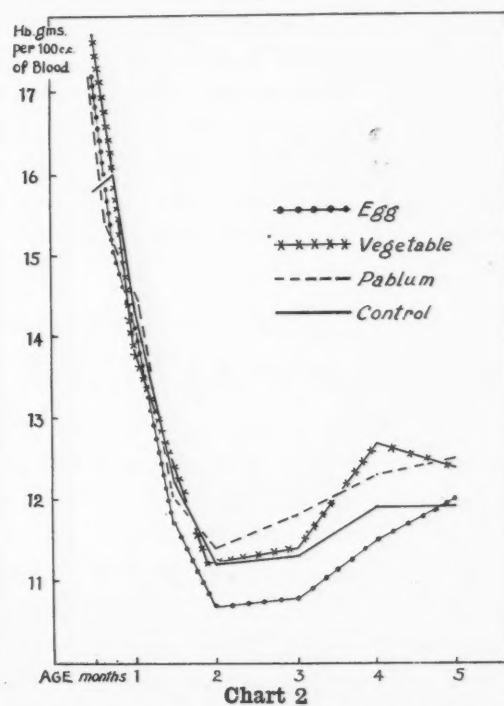
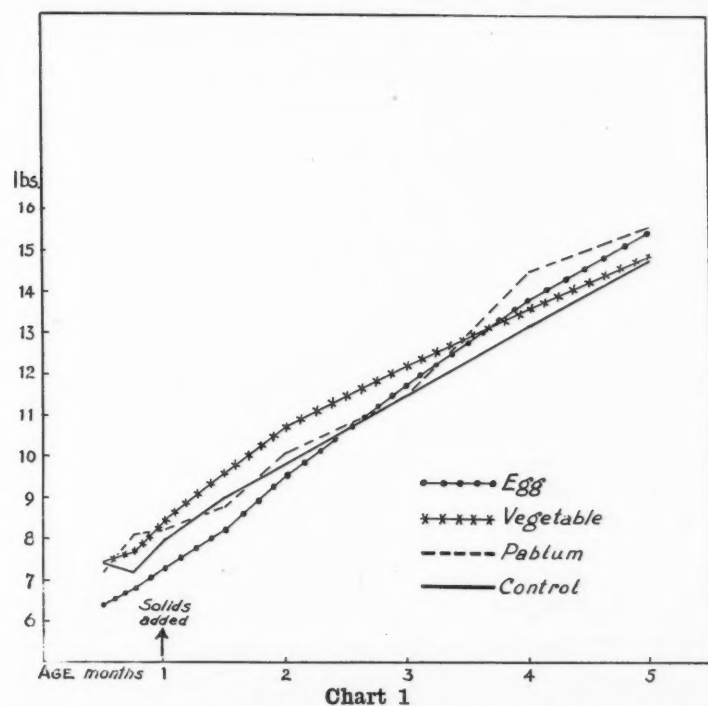


Chart 1.—A comparison of the average weights of four groups of normal infants from ½ to 5 months of age. One group (control) received milk feedings only. From the age of one month a second group received egg supplement, the third received pabulum supplement, and the fourth vegetable supplement. **Chart 2.**—A comparison of the average hæmoglobin of four groups of normal infants from ½ to 5 months of age. One group (control) received milk feedings only. From the age of one month the second group received egg supplement, the third group pabulum supplement, and the fourth group vegetable supplement.

is shown the average weights of the infants in various groups from ½ to 5 months of age. The group receiving egg started at a slightly lower average weight. There was no great difference between the weight gain of the control group and that of the groups receiving supplementary feedings. In Chart 2 is shown the average hæmoglobin content of the infants' blood in the various groups from ½ to 5 months of age. It will be observed that there is a rapid fall from 2 weeks to 2 months of age. At 1 month of age,

mothers had had children previously, and many were very much pleased with the early addition of solids, particularly cereal. To them, solids represented food in a way that milk mixtures did not.

In the group of infants placed on egg only one seemed more contented with egg in the feeding than before, and in that case there were loose stools. Diarrhœa, vomiting and discomfort occurred following the addition of egg in too great a percentage of cases for one to feel that egg

should be added early to the infant's diet except with the greatest of caution.

In the group of infants on pabulum the addition improved disturbed stools, and in 2 instances was more effectual than protein milk in correcting the stools. There was no laxative action. Many of the infants seemed more satisfied and slept better. The impression was that pabulum could be added to the infant's diet at 1 month of age with safety.

Vegetables given at 1 month of age to infants with normal stools did not cause looseness. Where the stools were previously constipated they were improved. However, no infant having loose stools at 1 month of age was placed in this group. It was felt unsafe to do so since in the author's previous experience the commencement of vegetables even at 5 or 6 months of age sometimes produced increased looseness of the stools in infants who were inclined to have intestinal disturbances. Discomfort did not follow the addition of vegetables, and sometimes the baby seemed more satisfied. The impression was acquired that vegetables could be safely added at this early age to the diet of infants with previously good stools.

SUMMARY AND CONCLUSIONS

A study has been made of feeding egg-yolk, pabulum, and canned sieved vegetables to infants from the early age of 1 month.

No difficulty was experienced in introducing vegetables and pabulum. When egg was added gastro-intestinal disturbances occurred in 41 per cent of the cases.

When either canned sieved vegetables or pabulum were started early the infants were more contented, the parents pleased, and other solids could be added with ease later on.

The addition of egg-yolk, pabulum, or canned sieved vegetables did not increase the weight or hæmoglobin over that of infants receiving milk mixtures alone.

Pabulum can be added with safety to the infant's diet from 1 month of age. In many instances the addition of pabulum to the diet improved the character of the stools.

REFERENCES

1. GLAZIER, M. M.: Advantages of strained solids in early months of infancy, *J. Pæd.*, 1933, 3: 883.
2. CALDWELL, G. W.: Nutritive value of strained vegetables in infant feeding, *J. Pæd.*, 1932, 1: 749.
3. POOLE, M. W., HAMIL, B. M., COOLEY, T. B. AND MACY, I. G.: Addition of vegetable soup and strained vegetables to diet of artificially fed infants, *Am. J. Dis. Child.*, 1938, 55: 1158.

THE USE OF COLLOIDAL ALUMINIUM HYDROXIDE IN THE TREATMENT OF PEPTIC ULCER*

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IN recent years there has been a tendency to avoid the use of absorbable alkalis in the treatment of peptic ulcer, and to search for antacid substances which do not affect the acid-base equilibrium of the body as a whole. Among these newer substances may be mentioned mucin, magnesium trisilicate, and colloidal suspensions of aluminium hydroxide.

The use of aluminium hydroxide in the treatment of peptic ulcer was introduced in 1922 by Roch, who reported favourably on its clinical use. Since this time a considerable number of clinical articles have been published. All of these have been favourable, and all attest to its value in relief of symptoms. Careful studies of its mode of action have also been made. The direct effect of the drug in controlling the acidity

of the stomach has been studied by several authors.^{1,2} A recent paper by Bennett and Gill³ presents clear-cut evidence that the free hydrochloric acid of the gastric secretion can be completely and continuously neutralized by its use. It is well established that aluminium is not absorbed from the alimentary tract. Evidence for this statement has been collected by Ivy *et al.*⁴ Einsel, Adams and Myers⁵ have shown that its use does not lead to alkalosis or other disturbance of the acid-base balance of the body. By inference one would expect that its ingestion would not be followed by "rebound" acidity or hypersecretion of acid, and it is generally agreed that such is the case. Indeed, Babkin⁶ found an inhibition of gastric secretion in dogs as an after-effect, rather than an increase. Similarly Einsel and his co-workers⁵ have presented evidence that prolonged ingestion of aluminium hydroxide cream by ulcer patients leads to a

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marked diminution in titratable gastric acidity after alcohol stimulation, in comparison with acidity curves determined before treatment was begun. Emery and Rutherford² have confirmed their findings. On the other hand, Einsel's conclusions have been criticized by Ivy *et al.*,⁴ who reported contrary results in dogs. Beazell, Schmidt and Ivy⁷ have found that the drug does not interfere with the activity of pancreatic enzymes *in vitro*, nor does it alter the nitrogen- or fat-content of the faeces. Woldman and Rowland⁸ have introduced a method of administration through a nasal catheter which has considerably increased its effectiveness in intractable cases and in hæmorrhage.⁹

The present report is based upon the clinical use of an aluminium hydroxide preparation* in 38 cases of peptic ulcer, some of them from the Out-Patient Services, the others from the medical wards. The group comprises all the cases which came under observation during a certain period, and in which the drug was used in adequate dosage for at least a week. Cases in which the diagnosis of peptic ulcer was in reasonable doubt have been excluded, as have cases in which ulcer was established but in which there was reason for attributing the symptoms to some associated condition, such as permanent pyloric obstruction or gall-bladder disease. A synopsis of the groups of cases and results of treatment is given in Table I.

TABLE I.

Group		Successful	Unsuccessful	Total
1	Out-patients....	7	0	7
2	Ward cases, uncomplicated....	18	1	19
3	Cases with gross hæmorrhage....	9	1	10
4	Cases complicated by infection.....	0	2	2
	Totals.....	34	4	38

Group 1. *Out-patients.*—This group of cases, 7 in number, comprises 6 cases of duodenal ulcer without complications, and one of jejunal ulcer, all proved by x-ray examination and showing evidence of active ulceration. The patients were allowed to follow their usual occupations throughout the course of treatment. In some

cases frequent feedings were advised, with milk freely used as an "interval" feeding; as improvement occurred, three regular meals were instituted, with restrictions. Aluminium hydroxide was prescribed, usually as two drachm doses, at first six times a day, later two or three times a day, as improvement occurred. All of these did well. The protocol of one of them is given below, to serve as an illustration.

CASE 1

J.D., 40, clothier, had been known to have duodenal ulcer ten years before, and had had recurrences of symptoms since that time. There had been severe periodic pain in the epigastrium for the preceding two weeks, with loss of weight. Gastric acidity was normal, and no blood was found in the stools. On roentgen examination the duodenal cap was deformed, and an ulcer crater was demonstrated. Sodium bicarbonate and Sippy powders gave him little relief, while the latter gave rise to diarrhoea, so that he was unwilling to continue them. The carbon dioxide combining power was elevated. When aluminium hydroxide was prescribed his pain was relieved and he no longer feared to eat. Within a week his non-protein nitrogen had risen from starvation level to normal. Within a month he had regained the weight which he had previously lost. The carbon dioxide combining power remained at a normal level throughout the period of treatment with aluminium hydroxide. When re-examined four months after the beginning of treatment, the duodenal cap was deformed, but no ulcer could be demonstrated. The chemical findings are summarized in Table II.

Several points of interest arise from the consideration of this small group of ambulatory cases. The patients took the preparation readily, and, even when due allowance is made for the possible effects of suggestion, seemed to experience marked symptomatic benefit. Five of the seven cases were re-examined after treatment had been continued for several months, and in none of these did an ulcer crater persist. In one case, in which an exploratory operation was carried out some time later, there was operative proof of cure. Only one complaint arose from the use of aluminium hydroxide. Several complained that it caused constipation. This was not sufficient to interfere with continuation of treatment, and was easily controlled by mineral oil. The literature makes frequent mention of this effect of the drug.

Group 2. *Ward cases, uncomplicated.*—This group of 19 comprises 15 cases of duodenal and 4 of gastric ulcer. Five were recent but the majority were of long standing. The average duration of the 14 chronic cases was ten years. Cases with intestinal obstruction or permanent pyloric obstruction have been eliminated, although six which showed some degree of gastric

* This work was supported by a grant from the John Wyeth and Brother Co., who generously supplied the preparation of aluminium hydroxide, known as "Amphojel", with which these studies were carried out.

delay have been included. These cases on the average are more severe and intractable than the ambulatory cases in Group 1. Hospital stay varied from one to ten weeks, though two to three weeks was the usual duration, not long enough to reach an opinion as to the final outcome of treatment. Some have been followed as out-patients and others by questionnaire, so that further information is available in ten cases.

The diet and dosage of aluminium hydroxide used in this group will be discussed below, along with the other groups of hospital cases.

treatment, although the immediate effect was considered to be good.

CASE 2

F.M., 52, boilermaker, had a history of recurrent attacks of indigestion and epigastric pain at intervals for 23 years. For a month there had been pain, intolerance of food, vomiting, and tarry stools. On radiography a duodenal ulcer was found, with a demonstrable crater. He was given sodium bicarbonate during the diagnostic period, then aluminium hydroxide cream, one drachm thrice daily, along with a milk and cream diet. After three weeks he left the hospital improved. Ten months later he called upon a surgeon, saying that medical treatment had given him no relief, and that he was prepared to submit to operation. When this was carried out a large ulcer was found, situated on the anterior wall of the duodenum, with an inflammatory process

TABLE II.

Case No.	Day of observation	Weight lbs.	Non-protein nitrogen mg. %	Carbon dioxide vol. %	Treatment prescribed	Remarks
1	1	122½	Sippy powders 6 times daily	
	5	..	14.5	70.1	" " 6 " "	
	7	122	16.7	72.0	" " 6 " "	
	15	123½	17.5	66.4	Aluminium hydroxide, 2 drachms, 6 times daily	
	22	124	25.3	69.2	" " 2 " 3 " "	
	29	126½	25.1	63.8	" " 2 " 3 " "	
	43	127½	" " 2 " 3 " "	
	57	127½	27.6	63.4	" " 2 " 3 " "	
	71	128	" " 2 " 3 " "	
	85	130	" " 2 " 2-3 times daily	
	106	131	" " 2 " 2-3 " "	
	141	130		Now completely symptom-free X-rays show deformed duodenal cap; no crater

As to the immediate effect of treatment this was very satisfactory. Pain was relieved usually in the first two or three days, and usually without the use of atropine or other drugs. It is difficult to apportion the benefit from bed rest, diet, and medication in judging this group of cases, except as a matter of personal judgment. With this qualification we may say that the immediate effect of the drug was very satisfactory indeed and compared favourably with any other form of medical treatment. On discharge all the patients were considered improved.

In eight of the ten cases in which follow-up information is available, progress has been satisfactory, although only one patient has been able to give up treatment altogether. One, under observation in the out-patient department, has suffered a recurrence of symptoms. She has stopped taking aluminium hydroxide on account of constipation, preferring an antacid which has a laxative effect. The tenth case must be regarded as a failure of medical

extending around it so that the duodenum was firmly attached to the pancreas. A partial gastric resection was done, with anterior gastro-enterostomy.

Group 3. Cases with gross hæmorrhage.—This group comprises nine cases of duodenal and one of gastric ulcer. One patient had no symptoms before the hæmorrhage which caused his admission. Like the previous group, the average duration of the chronic cases was ten years, and the usual hospital stay two or three weeks. Two of the cases were given Meulengracht's¹⁰ diet, the others "bland", or Sippy diets. Aluminium hydroxide was given by mouth usually every two hours, in one or two drachm doses. With one exception all the patients in this group did well. Hæmorrhage ceased, pain when present was relieved, and all were able to leave hospital improved. The protocol of the unsuccessful case follows.

CASE 3

M.J., 39, began to have periodic abdominal pain six years previously. A duodenal ulcer was diagnosed elsewhere, and confirmed by x-ray examination. He was treated at that time, and again two years later. A profuse hæmorrhage occurred the day of admission, fol-

lowed by tarry stools, collapse, and the vomiting of a large quantity of blood. He was given a diet of gelatine and lactose, to which cereal, milk and cream were added later. A drachm of aluminium hydroxide cream was given by mouth every two hours. For 17 days of his stay hæmorrhages continued to occur. The hæmoglobin was 83 per cent on admission, falling to 54 per cent two weeks later. There was persistent pain with only temporary relief after each dose of aluminium hydroxide. For this reason he was transferred to the surgical service, where partial gastrectomy was carried out. An active ulcer was found in the first portion of the duodenum, with marked œdema of the retroduodenal tissues, confirming the x-ray impression of a penetrating ulcer.

This series of ten cases is too small to reach a final conclusion as to the value of aluminium hydroxide given orally in the treatment of gastric and duodenal hæmorrhage. Woldman⁹ has reviewed the mortality rates reported in eight recent series of cases of hæmorrhage, and in these the fatalities have ranged from 10.7 to 22.6 per cent. In his own control series of 38 cases there were 11 deaths—a mortality of 28.9 per cent. Hence among our cases one to three deaths might have been expected, although none occurred.

Until recently medical treatment of hæmorrhage in peptic ulcer comprised starvation—withholding all solids and giving only ice-water by mouth, in order to avoid dislodging the clot by food or peristalsis. Meulengracht¹⁰ deserves great credit for breaking with this tradition, and allowing liberal meals to his cases of hæmorrhage; by so doing he reduced the mortality rate in his wards from 7.9 to 1.5 per cent. Alvarez and Carlson¹¹ suggest that the food neutralizes the acid of the gastric juice, and so protects the clot in the aperture of the bleeding vessel from digestion. Woldman⁹ points out that the optimum acidity for peptic digestion is between pH 2 and 3; about pH 5 the power of pepsin to digest protein disappears; and that blood clot placed in a test-tube with fresh gastric juice is protected from digestion by colloidal aluminium hydroxide, even at body temperature. This is the basis for the "drip method" which he introduced, which aims at complete and continuous neutralization of gastric acidity. In 21 cases of gross hæmorrhage treated in this manner he was able to report complete recovery in every instance. Comparing his results with those of our series, it would appear that Woldman's method is to be preferred to oral administration in cases of peptic ulcer which present this complication.

Group 4. *Cases complicated by infection.*—The two cases in this group were very much

alike. Both were in males in the fourth decade suffering from duodenal ulcer; one was complicated by chronic otitis media, the other by chronic pansinusitis. Aluminium hydroxide treatment over a period of months was unsuccessful in both instances. The experience with these two cases is in sharp contrast with the outcome in the preceding groups. It is well known that manifest infection of this type is a serious obstacle to healing, and calls for vigorous attention. In retrospect it seems that it was a mistake to attempt ambulatory treatment in these two cases, and that bed rest should have been advised, along with aluminium hydroxide administered by Woldman's "drip method".

DISCUSSION

The dosage of aluminium hydroxide used in these cases was either one or two drachms. Statistical examination shows that there is no advantage in the larger dose. It is difficult to generalize about the frequency of dosage. Thrice daily seems often enough to control symptoms and promote healing in some cases. In others it seems wise to begin with six doses a day, or even a dose every two hours. On the other hand there is an advantage in cutting down dosage as soon as the symptoms are under control, in order to avoid any tendency to constipation.

The difference in the properties of aluminium hydroxide and the readily soluble alkalies makes it important to consider the time of administration. The latter are commonly given about an hour after the meal, in order to control the peak of acidity. Aluminium hydroxide reacts rather slowly with acids, and much of its efficacy is lost if given an hour after food. Some of the patients discovered this fact for themselves, and preferred to take it immediately after eating. It is probably still better to give it half an hour before the meal, as advised by Kreis.¹² Ivy⁴ has called attention to the fact that the aluminium combines with the gastric mucus to form a flaky precipitate, which adheres to the mucosa of the stomach and duodenum. A film of this nature would serve as a physical protection to the mucosa and exert an antacid action as well. Hence it seems logical that the drug would have its best effect when given on an empty stomach.

No definite conclusion can be drawn from these cases as to the type of diet best given in conjunction with aluminium hydroxide, as failures were equally distributed between diets

of the Sippy type, and the hospital "bland" diet. It is fair to raise the question whether there is any need for diets of the Sippy type and the undernutrition incidental to their use, when the gastric secretion is modified by the presence of aluminium hydroxide.

The effect of aluminium hydroxide on the chemical composition of the blood is illustrated in Table III. Here 4 representative cases have

TABLE III.

Case No.	Day of observation	Dose of aluminium hydroxide per day, drachms	Non-protein nitrogen mg. %	Carbon dioxide vol. %	Remarks
2	11	70.7	Taking sodium bicarbonate. Duodenal ulcer; uncomplicated.
	12	3	19.2	61.3	
	13		19.6	61.3	
	14		20.8	56.3	
	15		20.0	63.7	
	16		19.6	60.4	
	17		23.5	55.1	
	18		22.0	55.5	
3	3	6	40.0	56.3	Duodenal ulcer; hæmorrhage.
	15		32.0	48.8	
	24		22.2	51.1	
	30		19.8	57.5	
	33		21.4	55.7	
4	2	3	Duodenal ulcer; uncomplicated.
	7		26.1	59.1	
	9		23.4	61.8	
	10		27.2	65.3	
	11		26.3	56.2	
	14		36.3	63.7	
	17		28.0	52.1	
	18		31.2	64.0	
5	1	3	Duodenal ulcer; uncomplicated.
	4		27.0	67.1	
	5		..	66.9	
	6		20.0	58.1	
	7		24.8	63.8	
	8		20.1	59.5	
	9		25.0	58.6	
	11		23.0	60.4	
	12		23.9	61.5	
	16		..	60.4	
	22		15.8	62.1	

been selected from 14 similarly studied. It is clear that there is no tendency to alkalosis or nitrogen retention, such as sometimes follows the use of soluble alkalis. If alkalosis is already present the carbon dioxide combining power tends to fall towards normal. Bennett and Gill³ have been able to put this preparation to a more rigorous test than it received in our cases. They were able to give two ounces daily to a patient with renal failure, without increase in the alkali reserve.

In this series of cases the symptomatic effect of aluminium hydroxide has been highly satis-

factory, and bears out the claims made for it in the literature. Its curative effect is probably measured fairly well by its value in relieving symptoms. If this is true it is fair to ask why so many patients state that they cannot give up its use, when they claim to be symptom-free. It is probable that fear accounts for the desire to continue its use. For this fear, of course, there is good basis, and occasional doses after dietary indiscretions or warning symptoms are probably of value in preventing relapse.

In this series there have been 4 definite failures in 38 cases (10.5 per cent). Einsel⁵ reported 9 failures in 110 cases (8.1 per cent), while Jones¹³ reported one failure in a group of 24 cases (4 per cent). In the cases recorded as failures, symptomatic relief was usually not satisfactory from the first. It is possible that some of these would have responded better to Woldman's method. It seems reasonable to consider that cases which have severe symptoms and long histories, and cases with radiographic or other evidence of penetrating ulcers should be treated in this manner, as well as cases with severe hæmorrhage.

CONCLUSIONS

It seems justified to conclude that aluminium hydroxide offers many advantages over the older remedies in the treatment of peptic ulcer and that its properties are such as to call for reconsideration of the principles involved. Hitherto, conventional treatment has been based upon a regimen of small meals, frequent feedings, the use of absorbable alkalis to control acidity and of atropine to control secretion. Each of these measures has its disadvantage. There is good evidence that frequent feedings are an undesirable stimulus to gastric secretion,¹⁴ and that absorbable alkalis lead to "rebound" acidity. It is fair to say that treatment by conventional methods has been a disagreeable ordeal, frequently made worse by hunger, deficiency states, and the symptoms of atropine poisoning.

It is evident that aluminium hydroxide has proved itself to be a highly effective antacid without danger of "rebound" activity. Although it may be used in conjunction with frequent feedings, these are no longer required to control acidity, and one may safely dispense with them if sufficient hydroxide is given. There is evidence that the drug has a tendency to inhibit gastric secretion when given over a considerable time. Finally, its use is compatible

with the present-day tendency to give more generous meals during treatment.

REFERENCES

1. CROHN, B. B.: *J. Lab. & Clin. Med.*, 1929, 14: 610.
2. EMERY, E. S. AND RUTHERFORD, R. B.: *Am. J. Digest. Dis.*, 1938, 5: 486.
3. BENNETT, T. I. AND GILL, A. M.: *The Lancet*, 1939, 1: 500.
4. IVY, A. C., TERRY, L., FAULEY, G. B. AND BRADLEY, W. B.: *Am. J. Digest. Dis.*, 1937, 3: 879.
5. EINSEL, I. H., ADAMS, W. L. AND MYERS, V. C.: *Am. J. Digest. Dis.*, 1934, 1: 513.
6. BABKIN, B. P.: Personal communication.
7. BEAZELL, J. M., SCHMIDT, C. R. AND IVY, A. C.: *Am. J. Digest. Dis.*, 1938, 5: 164.
8. WOLDMAN, E. E. AND ROWLAND, V. C.: *Am. J. Digest. Dis.*, 1936, 2: 733.
9. WOLDMAN, E. E.: *Am. J. M. Sc.*, 1937, 194: 333.
10. MEULENGRACHT, E.: *The Lancet*, 1935, 2: 1220.
11. ALVAREZ, W. C. AND CARLSON, L. A.: *Proc. Staff Meet. Mayo Clin.*, 1936, 11: 391.
12. KREIS, L.: *Wien. med. Wehnschr.*, 1931, 81: 140.
13. JONES, C. R.: *Am. J. Digest. Dis.*, 1937, 4: 99.
14. ALLEY, A.: *Am. J. Digest. Dis.*, 1934, 1: 555.

DYSMENORRHOEA*

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EXPERIENCES with a series of unselected cases of dysmenorrhœa seen in private practice in the last five years are summarized in this report. There seems to be urgent need for some etiological classification of dysmenorrhœa, and an attempt has been made here to present such a classification for this small group and to indicate a suitable type of therapy for each.

OUR DATA

Of the 130 women 86 were married and 44 unmarried. Their ages ranged from 14 to 48 years. There were 8 girls of 20 or under, 73 women of 21 to 30 years of age, 34 women who were 31 to 40 years of age, and 7 women over 40 years of age and still menstruating. The remaining 8 women were post-menopausal, and are included in this series because it represents all the women seen by the writer who had at the time or had ever had dysmenorrhœa. In so far as their recollections can be regarded as reliable they present an interesting sidelight on this problem—as to what can be expected in these cases without any attempt at treatment.

A systematic inquiry as to the presence or absence of menstrual regularity and the passage of clots was made. Moderate degrees of irregularity were often significant and are mentioned later in this paper. Many of the women spoke of having pain while expelling clots, but Gemmell¹ has pointed out that clots in the vagina are no proof that clots have been extruded from the cervix and, moreover, in 46

per cent of his cases clots were altogether absent. Most women's pain is premenstrual as well as intramenstrual, and certainly premenstrual pain could scarcely be ascribed to clots.²

Table I illustrates the variety of factors from which these women dated the onset of their pain or a severe aggravation of it.

TABLE I.

Puberty	100
Appendectomy	2
Miscarriage or abortion.....	2
Childbirth	2
Marriage	2
An unhappy love affair.....	1
Great business activity.....	1
Rupture of a cystic ovary.....	1
Indefinite, but onset later than puberty....	19

There was menorrhagia in 53 of these women, oligomenorrhœa in 14, and normal menstrual flows in 63.

Table II gives a list of the clinical diagnosis of these cases. It will be noted how many of these women suffered from a number of conditions, any one of which might possibly be blamed for menstrual pain.

As an adjunct to diagnosis we used blood œstrogen tests³ in order to determine whether or not this menstrual disturbance was associated with a corresponding modification of blood œstrogen levels. Obviously it was impossible to test all these patients, because many were seen in consultation, or but once, or demanded immediate therapeutic measures, or were seen only at times in their cycles distant from the menses. Sixty-three patients, however, were tested (Table III).

* Read at the Annual Meeting of the Ontario Medical Association, Hamilton, June 2, 1939.

TABLE II.

CLINICAL DIAGNOSIS IN THE 130 DYSMENORRHOIC WOMEN

Hypothyroidism only	34
Hypothyroidism + pelvic cellulitis	18
Retroversion	17
Sterility	17
Endometriosis	7
Hypothyroidism + retroversion	6
Fibroids only	5
Ovarian cyst	4
Adnexal inflammation only	5
Hypothyroidism + adnexal inflammation	3
Neurosis only	2
Hypertension only	2
Hypothyroidism + fibroids	2
Hypothyroidism + arthritis and neuritis	2
Hypothyroidism + chronic nephritis	2
Retroversion + adnexal inflammation	2
Hypothyroidism + pelvic cellulitis + underdeveloped uterus	2
Ureteral stenosis only	1
Varices of broad ligaments + adnexal inflammation	1
Hyperthyroidism only	1
Allergy only	1
Hypothyroidism + endometriosis	1
Hypothyroidism + peptic ulcer and habitual abortion	1
Hypothyroidism + neurosis	1
Hypothyroidism + arthritis + fibroids	1
Domestic strife + pelvic cellulitis	1
Chronic appendicitis	1
Allergy + fibroids	1
Infantile uterus + retroversion + hypothyroidism	1
Pelvic cellulitis + spine anomaly + ovarian cyst + hypothyroidism + retroversion	1
Chronic nephritis and hypertension	1
Hypothyroidism + hypertension	1
Hypothyroidism + pelvic cellulitis + dementia præcox	1
Pelvic cellulitis + neuritis	1
Hypothyroidism + neuritis + hypertension	1
No diagnosis made	24
All who had hypothyroidism	79
All who had retroversion	27
All who had pelvic cellulitis	24
All who had adnexal inflammation	11
All who had fibroids	9
All who had cystic ovaries	5

TABLE III.

	Menor- rhagia	Oligomenor- rhœa	Clinically normal menses
Excessive œstrogen	19	4	8
Subnormal œstrogen	1	1	8
Normal levels	7	3	12

When the œstrogen estimations were used as the sole indication for treatment these tests were correlated with the clinical result in 30 patients and disagreed in 4 cases; however, in 8 cases endocrine therapy was valuable where the œstrogen levels were normal. Therefore, it can be said that the assays were correlated with the therapeutic result in 71 per cent of cases. High values for blood œstrogens were found in 31 of the 63 women, it is to be noted. This agrees approximately with the figures of Kotz and Parker.⁴ Table IV summarizes the clinical results.

TABLE IV.

SUCCESSFUL TREATMENT USED

Thyroid extract only	47
Childbirth	19
Thyroid extract + pelvic short-wave	11
Marriage only	8
Estrogens only	7
Artificial castration	6
Prolan only	5
Wheat germ oil only	5
Lugol's iodine only	2
Progesterone only	2
Pelvic short-wave only	2
Suspension and resection of a cystic ovary	2
Spontaneous	2
Atropine only	1
Testosterone propionate only	1
Gonadogen only	1
Progesterone + salpingectomy only	1
Smith-Hodge pessary only	1
Abortion and miscarriage	1
Exploratory laparotomy only	1
Suspension only	1
Presacral neurectomy only	1
Appendectomy	1
Hysterectomy	1
Partial oöphorectomy	1
All those cured with thyroid alone or combined with other therapy	58
All those cured by the expulsion of a fetus	20
All those cured by anti-œstrogens other than thyroid extract	14
All those cured by œstrogens	8
All those cured by pelvic short-wave alone or combined with other therapy	13
All those cured by surgical methods or x-ray castration	15

These results may be summarized in this way. In the 130 patients 96 experienced "cure", 18 were greatly helped, and 16 experienced no relief. Of the "failures" 6 were patients who refused treatment. The percentage of failure was 12 per cent.

Perhaps it is worthy of mention that the therapeutic methods which failed oftenest were childbirth in 8 women, curettage in 5, uterine suspension in 4 and resection of an ovary with appendectomy in 3 patients. The author has never performed a uterine suspension. The cure after suspension reported above was obtained by another gynecologist in a girl revealing the histological appearance of endometriosis in an ovarian implant and extensive adhesions binding the uterine corpus in retroversion! This cure probably ranks with those reported of spontaneous regression of abdominal carcinoma after laparotomy. The writer never uses pessaries for the correction of uterine retroversion except in the very rare case of sterility; indeed, he ignores retroversion in his practice. This cure obtained by the use of a pessary was in a girl who had a freely mobile uterine corpus!

The writer uses the following simple classification in the consideration of dysmenorrhœic patients.

- (a) Endocrine dysmenorrhœa—
with excess of blood œstrogen
with deficiency of blood œstrogen
- (b) Inflammatory dysmenorrhœa—
parametrial cellulitis
tubovarian inflammation
- (c) Mechanical dysmenorrhœa—
fibromyomata of the uterus
endometriosis
ovarian cysts
- (d) Mixed types.
- (e) Unclassified—
membranous dysmenorrhœa.

This classification leaves something to be desired, but it is practical and simple and at least has the merit of indicating that menstrual pain is not a clinical entity but a symptom of many diverse clinical conditions. Little attempt has been made to preserve such old terms as extrinsic and intrinsic dysmenorrhœa, or spasmodic and congestive, or even primary and secondary. These have little if any clinical applicability, and the modern work on the hormones has upset many of their implications.

ENDOCRINE DYSMENORRHOEA

Thirty-five of our patients fell into this division, but endocrine factors are in addition the commonest etiological agencies in the mixed type of dysmenorrhœa discussed below. Gross irregularity of the menses is sometimes associated with dysmenorrhœa, and cure often coincides with a return to regularity through the use of endocrine therapy. Such frank irregularity probably is due to a derangement of the anterior pituitary control of the ovaries.

It has long been known, of course, that the clinical diagnosis of menstrual abnormality is not necessarily correlated with the underlying hormonal situation. For example, amenorrhœa or oligomenorrhœa may be as closely related to hypothyroidism as is menorrhagia, and may also respond to thyroid therapy. This defect of clinical analysis is brought out by Table III above. Therefore, it is more accurate to base one's therapy on blood œstrogen assays, but better still to rely on a proper mixture of clinical judgment and œstrogen analyses, an observation which of course holds true for any laboratory procedure. Conversely, however, œstrogen analyses are as valuable an adjunct to diagnosis and treatment in these problems as is the determination of blood sugar in the management of diabetes or of blood urea in the management of nephritis.

A point worthy of mention is that neither estimations of basal metabolic rate nor clinical observations on the quantity or duration of the

menstrual flow have helped in determining the dosage of whatever therapeutic agent has been selected for trial. One is forced to begin, in every instance, with a small dose and work up or down as clinical progress warrants. Indeed, the author has come to ignore the readings of basal metabolism very largely, and to rely solely upon the reaction of each individual to cautious therapy. This may at first sight appear to be a crude and unscientific approach to such a problem, but experience has shown that the patient is a more dependable barometer than any mechanical device.

INFLAMMATORY DYSMENORRHOEA

Six of our patients belonged to this class, but inflammatory lesions were common in conjunction with other types. Gonorrhœa does not bulk large in our private practice, and tubovarian inflammation is relatively rare. Backache, especially where it is the principal feature of the dysmenorrhœa, or develops following childbirth or abortion, is often due to pelvic cellulitis and responds to suitable physical therapy. Such cellulitis is common, and is to be detected most readily and oftenest in the utero-sacral ligaments.

MECHANICAL DYSMENORRHOEA

Sixteen of these women fell into this class. As has been pointed out, the author is prejudiced against ascribing dysmenorrhœa to retroversion or other such uterine malposition (a term that has questionable antecedents and a lamentable progeny). In none of his cases has a uterine suspension been performed by him, although 27 of the 130 had retroversion and in many cases this retroversion was "adherent". It is true that suspension had been carried out by other surgeons in five of the cases, but this had had little or no effect on the pain and the retroversion recurred in two of the five. One doubts if any operation but herniotomy is followed by a larger percentage of recurrence and certainly many women date their principal abdominal complaints from it.

Submucous fibroids may be difficult to detect except by curettage, for they may be too small to distort the corpus uteri very obviously. Indeed, the only indication for dilatation and curettage in the author's series of dysmenorrhœic women is the search for such fibroids when endocrine and other therapy has led nowhere and only these fibroids and endometriosis remain

to be excluded as etiological agents of the pain. An interesting case of this type of dysmenorrhœa was seen, where the pains of menstruation closely resembled labour pains, and finally the uterus was actually inverted in the effort to expel a small cornual fibroid.

Ovarian cysts are included in this class for lack of a better place for them. We know very little as yet of their etiology and so can scarcely estimate how they can be related to dysmenorrhœa—if there is anything more than coincidence in their occasional co-existence with the latter. Apparently they should be dealt with solely on their own merits in the effort to render the environment of the uterus as normal as possible, but the actual cure of the dysmenorrhœa is seldom to be ascribed to their surgical removal unless they represent concealed endometriosis. Indeed, most ovarian cysts even of large size are seldom associated with monthly pain.

Endometriosis produces some instances of the severest menstrual pain—or may be found with a complaint of little or none! Only 47 per cent of Counsellor's series had pain at the menses.⁵ It is doubtful if it should be classified as primarily mechanical or inflammatory or even neoplastic, for it partakes of the nature of all these conditions. It is being recognized much oftener than formerly, but generally offers great difficulty in diagnosis unless by biopsy at laparotomy. The pain may not be limited to menstrual periods, but may be felt as a constant or nearly constant lower abdominal distress, perhaps with tumour. Pain that develops only late during each menstrual flow or at its termination is especially suggestive of this condition. If the pouch of Douglas is involved there may be the gradual development of an adherent retroversion with pain during bowel movements. Acquired dyspareunia as well as painful nodules in the cul-de-sac have been mentioned in the literature as significant.

MIXED TYPES OF DYSMENORRHOEA

Fifty-one women were so classified. Indeed, it can be seen from Table II that dysmenorrhœa is usually a problem with multiple facets. Much the commonest clinical diagnoses were hypothyroidism, pelvic cellulitis, adnexal inflammation, and pelvic tumours. Similarly Table IV shows that the commonest agencies of successful therapy were hormones, physiotherapy, surgery or x-ray, and child-bearing. Dysmenorrhœa is a symptom not a syndrome. Therefore it is

optimistic to the last degree to think that any single method or product will "cure dysmenorrhœa". Many therapeutic agents are helpful, but to be successful must be freely mixed with medical brains.

UNCLASSIFIED TYPES OF DYSMENORRHOEA

No cause was found for the pain in 24 women. Some of these were cured by childbirth or marriage or spontaneously. Some represented our failures. It is in this group that presacral neurectomy plays an important rôle in treatment. We have used it just once, but almost certainly have been too sparing in so doing. It is important to point out, however, for what a small group of cases it is indicated. As Table IV shows all but 12 per cent of the 129 patients handled without it were cured or greatly helped. Of the remainder one-third refused treatment that was definitely indicated and should have been of great benefit. It would appear, therefore, that fewer than 10 per cent of dysmenorrhœic women require such treatment.

THERAPY

It should not be necessary to insist that diagnosis should precede therapy where possible. Yet it is a commonplace that the majority of dysmenorrhœa cases are treated by one method or another without any careful and adequate attempt at diagnosis. Table II would indicate that the diagnosis of many of the pathological conditions at fault should be simple, especially if one recognizes the numerous cases of occult hypothyroidism seen in this part of Canada.⁶

If thyroid extract be used in therapy the dose should be raised to tolerance or near it, with due regard for seasonal modification in dosage and the fact that treatment must be continued indefinitely. Where œstrogens were indicated the author has generally used hypodermic injections of progynon B, kindly supplied by Schering and Company, and, more recently, gonadogen, supplied to him for experimental purposes by the Upjohn Company. This is one of the conditions in which an intravenous œstrogen is a real desideratum. Treatment, again, must be continued each month in almost every case. The pregnant mare's serum (gonadogen) is similar to, if not identical with, the follicle-maturing factor of the anterior pituitary, and I have used it to induce the patient's own body to produce higher levels of œstrogen before the menses in eight cases of the low-œstrin type of dysmenor-

rhœa. It has consistently done so, and I have seen no unfavourable reactions to its use. Because it appears to be a more physiological approach to this problem, it sometimes alleviates *Mittelschmerz* and mid-interval or intra-menstrual headaches better than the œstrogens themselves. It has to be remembered, of course, that it is a horse serum derivative, to which some women may be sensitive. I have not included more of my treated cases in this study because at present I am studying the duration of its effect. The doses found most satisfactory have been at least 20 rat units given every four to five days in the first half of the cycle.

Prolan preparations, whether made from early pregnancy urine or placenta, are of especial value when a patient is seen for the first time during her pain. They take effect relatively quickly. Sometimes the curative effect lasts for months or longer. Progesterone is valuable similarly, in milligram doses. Testosterone propionate in doses of 10 mg. seemed less useful in one case of ours. Wheat germ oil acts much like progesterone. Certain cautions about its instability and the method of dosage with initial saturation must be observed.⁷

We have never used the Elliott bag for giving pelvic heat, but since using a short-wave machine for that purpose have given up all hot douches.

For endometriosis at any age castration by surgical procedures or x-ray or both seems desirable. The most interesting and trying cases are those whose pain is derived from widely different causes. For example, the author operated on a very early case of endometriosis involving only the left tube and ovary so far as could be seen. Accordingly, he removed just the left tube and ovary, but the patient continued to have severe pain at the menses—until thyroid extract up to four grains a day was administered. On another occasion, he removed a chronically inflamed right tube with complete relief of pain. But in a few months the pain had recurred. It was promptly cured by progesterone, and it in turn was replaceable with thyroid extract, on which relief has been permanent.

DISCUSSION

A survey of our case records reveals a number of significant features. For example, dysmenorrhœa is not, as is so often thought, restricted even in large part to single women and marriage of itself is rarely a cure for it. When marriage

per se does appear to result in relief, it can probably be said to be due to relaxation from the mental and physical tension of unsatisfactory single life. It is hard to understand how marriage can alter any endocrine factors that might be responsible for the distress. It will be noted that a few women, indeed, have increased pain with post-marital menstruation, and this, too, is not to be rashly ascribed to adnexal infection. It is more likely an evidence of new mental strain. The mechanism of psychic control of menstruation and its disturbances is no less puzzling now than a century ago.

Childbirth occasionally relieves painful menstruation, presumably more on account of the new and more normal mental and hormonal equilibria accidentally ensuing than because of any mechanical effect on the uterine musculature ascribable to birth traumata. Indeed, one finds women who complain either that childbirth had no effect at all on their distress or even seemed to aggravate it. This emphasizes the unimportance of mechanical factors in the cervix and also the unpredictability of such changes in hormonal balance as have just been mentioned.

Retroversion bulks large in this group of dysmenorrhœic women, as it would in any group of normal or abnormal women at any age. It takes courage, or rashness, or some mixture of the two, to challenge the usefulness of such an ancient procedure as the "correction" of retroversion by means of pessaries, exercises, or operation. It will be seen, however, that the author has blandly ignored retroversion in every case. In fact, he has yet to see a patient where retroversion was significant in respect to any menstrual dysfunction. A number of these women had had suspensions done before they consulted him. The general lack of results in this series after this procedure speaks for itself. It should at least be of interest that a series of these cases can be treated for pain at the menses without taking any cognizance of uterine position.

Many of our therapeutic results have been labelled "cured". What should we mean by the "cure" of dysmenorrhœa? The answer is really, at least for the endocrine factors concerned, much the same thing as is meant by the cure of cases of diabetes or hypothyroidism or adrenal cortex deficiency. The substitution therapy used is effective as long as it is used, but rarely any longer. Since many of these dysmenorrhœas appear to be related to an excess activity of the

endocrine centres producing oestrogens, our treatment in such women is the reverse of substitution, *viz.*, the use of anti-oestrogens, presumably as neutralizing agents. The effect of such measures is as transient as that of substitution therapy. In occasional individuals, however, the pituitary motor of the sex hormone machinery appears to be favourably influenced by substitution or inhibitory therapy and can carry along at its adjusted level of activity after therapy has ceased. These results are at present unforeseeable, and are all too rare. It is obviously important that patients should understand the need for continued treatment.

In the case of the inflammatory and mechanical cases "cure" has its traditional implication of permanence after the cessation of a short period of treatment.

There are some puzzling features about menstrual pain. In some women the menstrual distress is accompanied by a "premenstrual tension", which may be more distressing than the actual pain. Progesterone helps this frequently. A few women do not have pelvic dysmenorrhœa, but pain, felt, for example, only in the thighs or knees. Why this should be either unaccompanied by or related to pelvic pain is not clear. With other patients headaches are the principal feature of the menstrual distress. These symptoms, which indicate that menstruation and its derangements are constitutional phenomena as well as local, often respond to the treatment of dysmenorrhœa as indicated above. Light is cast on them by some of the recent observations of Brewer⁸ on capillary vasospasm in the skin associated with severe dysmenorrhœa.

Many women use the idiomatic term "cramps" when discussing their menstrual distress, but on closer questioning this is usually found to refer to a constant pelvic pain or low backache, rarely with superimposed intermittent exacerbations. It has been relatively rare in our experience to get a history of intermittent pains only. It seems impossible to correlate the patient's report of her sensations with her blood oestrogen values, which in their turn appear to be related more or less closely to the quality of the spontaneous contractions which the uterus undergoes just before and in the early part of menstruation. Moir⁹ has noted that the pain experienced by the patient is not necessarily correlated with the intensity of the uterine contractions. Moreover, the powerful contractions of the uterus in late

pregnancy are painless. Puerperal uterine contractions, too, may be strong and frequent and yet be scarcely perceived. It is difficult to understand how uterine contractions, however abnormal, can be responsible for dysmenorrhœa, therefore, and Lackner and Krohn appear to have proved definitely that menstrual pain can be developed in the absence of any such contractions at all.

THE ETIOLOGY OF DYSMENORRHOEA

There must be many widely different causes for menstrual pain, as our classification attempts to indicate, even in the same person. In about half the cases of endometriosis the pain appears to be due to bleeding into small spaces bounded by dense walls of myometrial tissues, ovarian stroma, or other such visceral structures, or adhesions. In other cases the bleeding is not so confined, and does not give pain. Submucous and intramural fibromyomata may irritate the uterus like foreign bodies. Pelvic inflammations producing pelvic congestion and induration are obvious causes of menstrual pain where present, of course.

Endocrine derangements seem to be the most fertile cause of menstrual pain, however, although the exact mechanism of the dysmenorrhœa may be obscure as yet. Much of our recent knowledge of uterine physiology is due to the studies of S. R. M. Reynolds.¹⁰ He demonstrated that oestrogens induce motility in the uterine muscle associated with marked hyperæmia and œdema. A somewhat similar motility is produced by myometrial inflammation.¹¹ The motility due to oestrogenic activity is preceded by a great dilatation of the vessels comprising the vascular bed of the endometrium, and this congestion coincides with a rapid elevation of the oxygen consumption of the uterine tissues.¹² Of course, the idea advocated by Moir and others that excessive uterine contractions are the common cause of endocrine dysmenorrhœas is not applicable to the low œstrin types with slight or no uterine contractions during the pain. This point has been generally ignored by those formulating theories of the endocrine causation of functional dysmenorrhœas. Lackner and Krohn found large uterine contractions similar to those detected in the high œstrin dysmenorrhœas in women who experienced no menstrual pain, and on the other hand relieved the distress of two dysmenorrhœic women of this type with pro-

gesterone without affecting the uterine motility. Moreover, these workers found no definite correlation between the type of the endometrium and dysmenorrhœa. Fluhmann¹³ concludes his study of this problem with the remark that "There are serious objections to accepting any of the theories which seek to explain the cause of primary dysmenorrhœa solely as a deficiency or excess of either œstrogen or progestin".

Membranous endometrial exfoliation was first described in 1779 by Morgagni, and is often characterized by excessive dysmenorrhœa. This is not always the case, however.¹⁴ Beckwith Whitehouse¹⁵ in 1926 advanced the proposition that the outstanding feature in dysmenorrhœic menstruation is the casting off of endometrial "flakes" in mild cases or of "placques" or "casts" in the severe ones. He thought membranous dysmenorrhœa just a severe grade of a common condition. The severity of the pain varied directly with the amount and size of the solid tissue fragments. Bartelmez¹⁶ pointed out that macroscopic fragments of endometrium may be passed during normal menses. These are blood-soaked and probably are due to detachment of whole areas after massive hæmorrhagic extravasations. Uterine epithelium was cast off in 50 per cent of women on the first day of the menses, 74 per cent on the second day, and 54 per cent on the third day. Novak and TeLinde found only the decidua basalis left in a human uterus on the third day of flow. Bartelmez points out that no adequate studies of the uterine or ovarian nerve endings have yet been made. What studies have been made are recorded by Davis.¹⁷ He quotes Markee's unpublished work on endometrial transplants to the eye, indicating that the uterine mucosa is always blanched before the onset of flow, then later develops hæmatomata about some of the arterioles with ischæmic areas

between. No detachment of tissue particles occurs for the first 12 hours of menstruation. Finally toward the end of the menses arteries with necrotic tips project into the uterine lumen, says Bartelmez. One wonders if occasionally sensitive nerve filaments are not similarly exposed if the endometrial sloughs happen to be especially deep.

Such agencies as neurosis, intra-uterine clotting, uterine malposition and malformation, cervical stenosis, faulty posture, and anæmia, which have in turn attracted attention in the past, can now be relegated into very insignificant rôles. Mechanical and inflammatory causes undoubtedly are significant, as our classification indicates. But endocrine causes play a major rôle, as has been recently recognized.

REFERENCES

1. GEMMELL, J. E.: Intrinsic dysmenorrhœa, *J. Obstet. & Gyn. Brit. Emp.*, 1923, 30: 230.
2. CANNON, D. J.: Modern theories of dysmenorrhœa, *ibid.*, 1936, 43: 492.
3. SHUTE, E. V.: Determination of the œstrogenic substance in blood serum by means of an estimation of the anti-proteolytic power of the serum, *Am. J. Obstet. & Gyn.*, 1938, 35: 970.
4. KOTZ, J. AND PARKER, E.: Endometrial patterns in dysmenorrhœa, *ibid.*, 1939, 37: 116.
5. COUNSELLER, V. S.: Endometriosis; a clinical and surgical review, *ibid.*, 1938, 36: 877.
6. SHUTE, E. V.: Menorrhagia, with especial reference to occult hypothyroidism, *Canad. M. Ass. J.*, 1938, 41: 115.
7. *Idem*: Wheat germ oil therapy; preservation of potency; influence on labour; seasonal needs, *Am. J. Obstet. & Gyn.*, 1938, 35: 609.
8. BREWER, J. I.: Rhythmic changes in the skin capillaries and their relation to menstruation, *ibid.*, 1938, 36: 597.
9. MOIR, C.: The pain of labour, *The Lancet*, 1939, 1: 886.
10. REYNOLDS, S. R. M.: The nature of uterine contractility: a survey of different trends, *Physiol. Rev.*, 1937, 17: 304.
11. LAUFER, M. W. AND REYNOLDS, S. R. M.: Uterine motility resulting from inflammatory processes in the myometrium in the absence of ovarian hormones, *Am. J. Obstet. & Gyn.*, 1938, 35: 825.
12. REYNOLDS, S. R. M.: Acetylcholine content of uteri before and after administration of œstrin to ovariectomized rabbits, *J. Physiol.*, 1939, 95: 258.
13. FLUHMAN, C. F.: The period of puberty and the inception of menstruation, *Am. J. Obstet. & Gyn.*, 1936, 31: 573.
14. BLAIR BELL, W.: Intrinsic dysmenorrhœa, *J. Obstet. & Gyn. Brit. Emp.*, 1923, 30: 119.
15. WHITEHOUSE, B.: A contribution to the pathology and causation of dysmenorrhœa, *ibid.*, 1926, 33: 607.
16. BARTELMIZ, G. W.: Menstruation, *Physiol. Rev.*, 1937, 17: 28.
17. DAVIS, A. A.: Innervation of the uterus, *J. Obstet. & Gyn. Brit. Emp.*, 1933, 40: 481.

THE COMMON COLD.—While physicians admit that much remains to be learned about the common cold, they are now pretty sure that colds are caused and spread by an organism which they cannot see and to which they have not given a name. It belongs to the class of sub-microscopic organisms known as "filterable viruses" because they are small enough to pass through a porcelain filter, which will catch ordinary bacteria. Our friendly, gregarious habits make the travels of this virus extremely rapid. We sneeze in crowded rooms, and the virus rides the air on tiny droplets until the next victim breathes it in. We blow our noses politely and then shake hands with a friend, who later takes a pencil in that hand and

puts it to his mouth. Or we kiss and give our love and our virus, too. Or we leave it on doorknobs for the next comer. As for treatment, the doctor's recommendations are simple: Take a hot bath, get to bed, eat lightly, drink plentifully, keep your bowels open, and call in the doctor if you feel the need of medication. However, the majority of people prefer to disregard this advice, for it is much less colourful and interesting than the home remedies which are so numerous—remedies which include gym workouts, lemon juice ("to build up the white corpuscles"), quinine, laxatives, chest ointments, mustard baths, chiropractic treatments, boiled onions—and many, many more.—L. M. Miller in *Hygeia*, January, 1940.

THE MODERN TREATMENT OF NERVOUS SYPHILIS*

BY ALBÉRIC MARIN

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WE consider that a patient is suffering from nervous syphilis the moment his spinal fluid gives a positive reaction, even if he does not show any clinical sign of nervous or mental disturbances. The modifications of the liquid can be seen months and even years before the onset of the clinical manifestations. If not treated by proper methods the patient will present later on obvious signs of dementia paralytica, of taboparesis, of ataxia, etc. At these advanced stages the chances of curing the disease are greatly impaired. On the contrary, if an early diagnosis is made the prognosis is vastly improved.

This early diagnosis can be made only by a systematic spinal fluid test in every case of old syphilis. In our Department of Syphilology a routine spinal puncture is made. Thus we have discovered a large proportion of early nervous syphilis, with no clinical signs, where an immediate treatment gave far better results than if it had been given at a more advanced stage when mental troubles are manifested. We cannot emphasize too much the importance of the spinal fluid examination.

Nervous syphilis does not respond to the ordinary anti-luetic treatment. Neo-arsphenamine, bismuth or mercury cannot stop the action of the treponema when it has reached the nervous system. These drugs, even given in a high dosage and for a long period of time, cannot arrest its evolution. However tryparsamide or stovarsol in certain cases gives good results, but generally their efficiency is inferior to other methods of treatment.

Nervous syphilis was practically incurable until treatment by malarial fever was introduced in modern therapeutics. Up to about twenty years ago a patient suffering with general paresis, even with the best treatment of those days, had no chance of recovery. Malaria therapy has changed the prognosis of this disease. Partial or full remissions, permanent or temporary, have been obtained. The proportion of cures is much greater if this treatment is given at an early date. Cases treated at the onset give a higher rate of cures than those treated at a more advanced stage. At the pre-

clinical period, when we deal with asymptomatic nervous lues with only a positive spinal fluid, results are still better. This explains the apparent contradiction of certain statistical reports. Those who come from a Department of Syphilology where the majority of patients are seen before they develop mental troubles will naturally be better than those from an insane asylum. In Vienna with 2,000 patients treated with malaria 32 per cent of full remission were observed and 12 per cent of partial remission. The death rate was about 12 per cent.

In our Department of Dermatology and Syphilology at the Notre-Dame Hospital we have treated 144 cases with malaria with 6 deaths, which is a proportion of 4 per cent. We have obtained 40 per cent of full remissions, which is superior to the statistics of an insane asylum for the reasons given above.

But malaria therapy has also some disadvantages. Its contraindications are numerous—old age, poor general condition, heart trouble, low blood pressure, anæmia, diabetes, etc. Many patients who are given malaria will during its course present alarming signs which will force us to stop its evolution. Quinine has to be given immediately to prevent a fatal outcome, if not too late. Malaria causes anæmia, loss of weight, and necessitates a convalescence of around a month. It requires a stay in hospital from 6 to 8 weeks, which for certain people is too onerous.

On account of these disadvantages, since about 10 years ago various experiments have been conducted in several clinics to replace malaria inoculations by other methods, to improve the results and lower the death rate. Sodium nucleinate, sulphur, different vaccines giving shock and temperature, were used, but their results, good in certain cases, were not so high as those of malaria. Finally, the method of chemo-pyreto-therapy has been established, which is a combination of arsenic-bismuth treatment and artificial fever given by physical agents (short waves or hot moist air).

With artificial fever there is no effort on the part of the organism to raise its own temperature; on the contrary, the only reaction which one will observe on the part of the organism will be to become cooler (Richet). The patient's only

* Read at the Seventieth Annual Meeting of the Canadian Medical Association, June 22, 1939.

effort is to perspire heavily and to breathe more rapidly. Hence the mechanism of the heat is quite different in both cases. With artificial fever the rise of the temperature is passive, with malaria or chemical and biological means it is active.

If we compare temperature charts of patients treated with malaria and those treated with artificial fever we see at a glance that the total amount of a high temperature is far greater with those treated by artificial fever. A patient, for instance, treated with malaria will be allowed to have 8 to 10 crises, some of them giving a temperature of 105° , even 106° , but staying at this peak for only about one hour and followed by defervescence. So, finally, that patient has kept a temperature of 105° during only 8 or 10 hours. A patient treated by artificial fever will be submitted to a temperature of 105° for 50 hours, divided into 8 or 10 sessions. It is logical to believe that the mode of action of artificial fever and malaria therapy is quite different. In one case there is a high and prolonged passive heat (50 hours); in the other there is a moderate amount of heat (10 hours).

Artificial fever, given alone, does not give as good results as when combined with chemo-therapy. Generally the method of chemo-pyretotherapy is used, but, personally, we thought it might be more beneficial to the patient if we added vaccines to arsenic and artificial fever. This protein-therapy associated with hyperthermia would give a biological reaction which would add to its efficiency. We thought there would be a certain advantage in uniting in a same therapy modes of action which are not identical, that the combination of vaccines-drugs-heat would intensify it; the vaccine will produce a shock, the high temperature will lower the resistance of the treponema, and arsenic will bring its specific action.

Therefore we have established the following routine of treatment. On Monday, for instance, the patient receives at 7 a.m. an injection of tryparsamide and is immediately given a treatment of 5 hours of artificial fever at 105° . On Wednesday and Friday he gets an injection of fever-producing vaccine (such as Dmelcos or Pyrifer) and of bismuth. These vaccines give an average temperature of 103° .

The same procedure is repeated for 10 weeks. This will give a total dosage of 50 hours of artificial fever at 105° , 10 injections of tryparsamide and 20 injections of vaccines and

bismuth respectively. The patient is then treated at the Out-Door Clinic. At Notre Dame Hospital, we have been using the method of chemo-vaccine-physico-pyreto-therapy for 20 months. Our results so far are very satisfactory.

This treatment is not so weakening as malaria. As a matter of fact, in many instances it requires an hospitalization of only a day per week, the patient going back home the day following the artificial fever treatment. Many of our patients could even carry on with their usual work, coming to the hospital only for the artificial fever treatment. This consideration is very important for those unfortunates who are not able to pay the cost of a stay of about 6 weeks in hospital, which is the average time required for malaria therapy.

Our death rate is much lower, despite the fact that we have submitted to artificial fever patients we would not have dared to treat with malaria. We gave the full artificial fever treatment to adults up to the age of 55 years, even to a pregnant woman, with only one death in 174 cases. This gives a death rate of about one-half of 1 per cent, to be compared with 4 per cent with malaria. We have already given 5,600 hours (in 970 sessions) of a temperature of 105° .

Of these 174 cases 65 are kept for this study. The others for various reasons have been eliminated. Some did not come back for the following treatment; others refused to have a second spinal fluid test or were not seen.

These luetic patients had a spinal fluid examination immediately before the treatment and another immediately after. Out of these 65 patients, 35 showed a well defined improvement of all the reactions at the second spinal fluid examination, giving a proportion of 53 per cent.

In 27 patients a third spinal fluid examination was made in an average time of 9 months after the combined artificial fever therapy. Five gave a negative result (18 per cent).

Of these 65 luetics, 32 were mental cases: 15 had a complete remission (47 per cent), 9 had a partial remission (28 per cent).

In conclusion, we think that the combination of arsenic-bismuth, vaccines and artificial fever (chemo-vaccino-pyreto-therapy) constitutes a well marked improvement over other methods, being less dangerous, more effective, and more economical.

INTERPRETATION OF THE FACTOR OF LATENCY IN SYPHILIS*

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THE diagnosis of latent syphilis is made largely by the exclusion of obvious and of ill-defined late syphilitic manifestations, by negative results obtained in certain laboratory manoeuvres, by the interpretation of the time- and sex-factors, and by prolonged periods of observation. The term "latency" is a relative one, and while it is generally assumed to indicate a dormant or inactive process this is very rarely the case. It has been defined by O'Leary¹ as "that phase of the disease in which neither symptoms nor signs are present".

Latency may be clinical (without symptoms), serological (active pathological lesions with negative serological tests), or pathological (in the sense of absence of cellular reaction to spirochaetes). Yet all of these phases of latency are relative rather than absolute fixed states. Often ill-defined symptoms or syndromes suggesting other disease are present, and, while these are undoubtedly frequently non-syphilitic in nature, a possible syphilitic etiology is usually ignored, and very commonly the positive serological test, the penile scar, or the history of previous syphilis, escape detection.

True serological latency is to a considerable degree a function of the sensitivity of our complement fixation and precipitation tests. The older and less sensitive serological test resulted in a much higher proportion of cases of serological latency than is now seen. With further increases in sensitivity the number will probably become even smaller. It should be recalled, however, that there is a definite and spontaneous tendency for the blood, and to a lesser extent the spinal fluid, to become normal during the evolution of the disease.

If we are to accept Warthin's² necropsy studies of a large series of patients with latent syphilis, the term "pathological latency" can also be used only in a relative sense. The pathological threshold is definitely lower than

the serological and clinical ones, and Warthin was able to demonstrate that practically 100 per cent of syphilitic patients, treated and untreated, still showed evidence of pathological activity at autopsy. Permanent clinical arrest and serological reversal are not incompatible with low grade pathological activity. For example, Warthin found that about 85 per cent of latent syphilitics showed focal meningeal thickenings and infiltrations, yet none of these patients had ever developed evidences of clinical neurosyphilis. Thus all degrees of pathological activity can be assumed. At the one extreme is the well, arrested case, while at the other is the frank manifestation of late, visceral, syphilis. Then there is an in-between group of patients with either occult or sub-clinical syphilis, or with vague complaints or ill-defined syphilitic entities. It is with this in-between group of cases that the present paper is concerned.

CASE 1

N.E., an English Canadian woman of 30 years was found to have a positive blood Wassermann reaction. The physical examination, cerebrospinal fluid examination, the examination of the heart and great vessels, and fluoroscopy were entirely negative. During a 4-year period she was given 52 injections of bismuth and 47 of neosalvarsan, during which time the blood Wassermann reaction remained strongly positive. She was subsequently followed during a 4 year-period with no demonstrable change, and in good general health.

CASE 2

B.L., an English Canadian woman of 48 years was seen in the Clinic because of the presence of congenital syphilis in her 18-year old daughter. Physical examination, fluoroscopy and examination of blood and cerebrospinal fluid were entirely negative. The duration of the disease was roughly fixed at 28 years. It was felt that the patient was an example of true latency, and no treatment was given. Follow-up for a subsequent period of 3 years revealed no change.

CASE 3

G.A., a white man, aged 64 years, was treated elsewhere seven years previously because of the possibility of syphilitic myocarditis. His only complaints had been slight malaise and undernutrition, with an irrelevant past history. The blood Wassermann reaction was positive. Despite the assumption of a possible syphilitic myocarditis, treatment was begun with neosalvarsan. That syphilitic myocarditis was not present was suggested by the absence of immediate

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cardiac complications, but a severe post-arsphenamine dermatitis developed after the eighth injection. Five years later, because of the persistent positive blood Wassermann reaction, bismuth therapy was instituted, but another severe exfoliative dermatitis was precipitated. After a year's rest, despite the previous complications, thirty-two further injections of bismuth were given, but were finally stopped because of the development of a chronic eczematoid dermatitis of the hands. Two months later mercury and iodides were begun, but a scarlatiniform mercurial eruption soon appeared and the patient was referred to the clinic for further treatment.

Examination revealed no evidence of active syphilis. The heart was somewhat enlarged, the blood pressure was 190/120, and the electrocardiogram revealed evidence of myocardial degeneration. The blood Wassermann reaction was strongly positive; cerebrospinal fluid examination, negative. Since no evidence of activity could be found the patient was placed under observation, and a routine follow-up over a four-year period has shown no change in physical signs, x-ray, or electrocardiographic findings.

These patients illustrate some of the problems commonly met with in the management of latent syphilis. In all three the infection was apparently inactive, yet in Case 1 thorough treatment was given, the age of the patient and the duration of the infection not precluding the possibility of infectivity to future offspring, or the development of complications referable to syphilis. Approximately 35 per cent of patients with latent syphilis will have irreversible blood Wassermann reactions and yet otherwise remain in excellent health. Every comparatively young patient must be treated to avoid complications, particularly of the cardiovascular system. In contrast, the second patient was beyond the child-bearing period, and the duration of the infection rendered the development of late changes improbable, since most of the complications develop within twenty years after the onset of latency.

In the third case the combination of physical signs and positive blood Wassermann reaction led to the erroneous diagnosis of active syphilitic heart disease, and treatment was energetically pursued in the face of repeated complications. In spite of the persistence of the positive blood Wassermann reaction, the latency of the syphilitic infection was established by absence of progression over a four-year period, as determined by repeated physical examinations, electrocardiography and orthodiagraphy, and absence of clinical progression.

CASE 4

J.L., a white man, aged 42 years, sustained a crushing injury to the right great toe in November, 1936. Osteomyelitis with secondary sinus formation developed which failed to heal under repeated surgical intervention over a three-months' period. A long-standing syphilitic infection was considered as a

factor in the indolence of the local process, and he was referred to the clinic. Physical examination showed no change. There was no evidence of peripheral syphilitic arteritis, local gummatous change, or *mal perforant*, although the cerebrospinal fluid examination showed a slight increase in cell count, a strongly positive Wassermann test, and a low luetic gold curve. A therapeutic test was instituted with mercury and the lesion healed in three weeks.

In this instance the syphilitic infection, in the absence of specific lesions, undoubtedly exerted a deleterious influence on the healing of the local process. This unfavourable influence of an apparently latent syphilis upon the course of other disease has been designated by Wile³ as subclinical or occult syphilis. The activity obtaining in clinical latency is often sufficient to light up an inactive tuberculosis or to lower the resistance of the host to an initial tuberculous infection. Similarly, the presence of a long-standing syphilitic infection, with attendant leukoplakia or visceral scarring, may, in the face of further irritant effects, definitely predispose to carcinomatous change. Its importance is also recognized as a factor in the non-resolution of pneumonic processes, chronic upper respiratory infections, and obscure fevers.⁴

CASE 5

J.A., a white man, aged 39 years was examined because of a latent syphilitic infection in the marital partner. The past history revealed multiple penile ulcerations sixteen years previously for which no treatment was given. There had been slight difficulty in initiating urination during the past six months. On admission to the clinic physical examination revealed small, unequal, and slightly irregular pupils, which reacted minimally to light. The knee jerks were slightly diminished and Rhomberg's sign was questionably positive. The blood Wassermann reaction was positive. The cerebrospinal fluid findings were as follows: Wassermann, 444; colloidal gold, 232100000; cells and protein normal. Examination was otherwise negative. Antisyphilitic treatment with old salvarsan and bismuth was instituted and the bladder symptoms disappeared.

This patient regarded himself as normal, and only a thorough physical examination, followed by study of the cerebrospinal fluid, revealed that active neurosyphilis was present. It should be recalled here that if a diagnosis of latency is made without examination of the cerebrospinal fluid fully 15 per cent will develop clinical neurosyphilis, and that this may be in a large part prevented by adequate treatment of the syphilitic infection in its asymptomatic phases.⁵

CASE 6

B.P., a white woman, aged 38 years, had complained of nausea and vomiting with the menses for several years. Two weeks before admission to the

hospital, and simultaneously with onset of menstruation, the vomiting had recurred and persisted without interruption until admission. Her past history revealed no evidence of previous syphilitic infection and was otherwise negative. The physical examination disclosed slightly unequal pupils, which reacted sluggishly to light, a moderate nerve deafness, and a blood pressure of 94/54. The blood Wassermann reaction was positive. The cerebrospinal fluid examination: Wassermann, 410; colloidal gold, 1121000000; a slight increase in proteins; and 12 cells. Prolonged treatment, consisting of alternating courses of old salvarsan and bismuth salicylate, was given, and the symptoms promptly disappeared. There has been no recurrence of the vomiting.

This case was first considered to be an endocrine disorder, and, had the cerebrospinal fluid not been examined, would have been considered as one of latent syphilis. The dramatic and permanent cessation of the symptoms was conclusive evidence that the neural axis had been actively involved by the syphilitic infection, and again illustrates the importance of cerebrospinal fluid examination before a diagnosis of latent syphilis can be made.

CASE 7

J.L., a white man, aged 48 years, was referred to the clinic with a probable diagnosis of late syphilis. He contracted syphilis in 1915 and was treated with twelve injections of old salvarsan and a comparable amount of heavy metal. A positive blood Wassermann reaction in 1919 was the occasion for ten injections of neosalvarsan, but the Wassermann reaction was unchanged. Vertigo developed in 1933 and further treatment was given with ten injections of neosalvarsan and ten of bismuth. The blood Wassermann reaction was still positive and the vertigo unrelieved. Polyuria was noticed in May, 1936, but was relieved by herniorrhaphy the following August. He then began to suffer from indigestion and recurrent upper abdominal pain, which was temporarily relieved by cholecystectomy the following year. In August, 1937, he developed headaches, pain in the back, weakness, and "lightning pains" in the extremities. There was some dyspnoea on exertion and palpitation during recent months. Shortly after there was a recurrence of the abdominal symptoms. Vertigo had been intermittently present since its onset. On examination no abnormalities were found and the blood Wassermann reaction and cerebrospinal fluid examination were negative. Electrocardiogram and x-ray of the heart were normal and an x-ray of the sinuses showed no disease. At the insistent request of the patient small doses of heavy metal were given with marked improvement.

An analysis of the above case reveals one outstanding feature, that of neurasthenia. The development of various symptoms was the occasion for antisyphilitic treatment and surgical procedures. The spontaneous reversal of the blood Wassermann reaction to negative, in conjunction with the negative results of examination, was highly suggestive of an inactive latent syphilis. The obvious mental and emotional instability, in conjunction with a marked interest

in syphilo-literature, was confirmatory evidence of a functional disorder.

CASE 8

G.C., a white woman, aged 47 years, was well until 1 year prior to admission, when she developed irritability and slight dyspnoea. Six days before admission vomiting occurred, followed by severe headaches, weakness, and frequency of the bowel movements. Examination revealed slightly irregular pupils and a slight weakness of the right angle of the mouth and of the right arm. Cardiac enlargement and hypertension were present. The cerebrospinal fluid was blood-tinged and under increased pressure. The blood Wassermann reaction was positive and the cerebrospinal fluid examination negative. Ophthalmoscopic examination showed arteriosclerosis and retinal haemorrhages. Despite the apparent latency of the syphilitic infection the possibility of cerebrovascular syphilis could not be eliminated, and active antisyphilitic treatment was instituted and continued over a two-year period. Two months later, while on a rest from treatment, she rapidly became unconscious. Examination revealed weakness of the right side of the face and complete flaccid peripheral paralysis with bilateral Babinski signs. The pupils were irregular and non-reactive. The spinal fluid contained gross blood and was under greatly increased pressure. Coma deepened and death occurred eight hours after admission. Autopsy revealed syphilitic endarteritis of the base of the brain, a ruptured aneurysm, the size of a pea, of the right internal carotid artery, located in the cranial aspect of the carotid foramen. Diffuse subdural and subarachnoid haemorrhage was present. There was a moderate syphilitic aortitis, while the kidneys showed hypertensive change. Despite the prolonged treatment the syphilitic process showed evidence of activity in the aorta and meninges, but the pathological changes in the aneurysm were extensive scarring and medial degeneration without cellular infiltration.

The active syphilitic process was in no way contributory to the death of this patient, the final vascular accident occurring in a scarred inactive area, from the stress of an increasing hypertension. While therapy in this case did not prevent the unfavourable outcome the occurrence of a previous vascular accident in a comparatively young syphilitic made treatment imperative, and the diagnosis of latent syphilis at least somewhat improbable.

CASE 9

D.G., a white man, aged 49 years, was in good health until two years previously, at which time he began to experience attacks of vertigo. For the past year he had suffered from epigastric pain, vomiting and stabbing pains in the ankles. He was examined elsewhere and a diagnosis of tabes dorsalis was made and treatment instituted. After six injections of bismuth, a course of neosalvarsan in a dosage of 0.6 g. was started. Early during the course of arsenical therapy he complained of increasing weakness and chest pains, and refused further treatment. On admission to the clinic definite signs of tabes dorsalis were present and the blood Wassermann reaction and cerebrospinal fluid examination strongly positive. Fluoroscopy revealed an aneurysm the size of a small orange situated in the upper portion of the descending aorta. Treatment was instituted with bismuth and tryparsamide, and his general condition became greatly improved. This improvement was only temporary, however, and he died a year later of rupture of the aneurysm.

In the presence of a demonstrable lesion in one system one is not justified in assuming that a state of latency occurs in other parts of the body. Wile³ has emphasized the need for a thorough evaluation of every patient with a long-standing syphilitic infection. In this patient the assumption that the nervous system only was involved probably contributed to the unfavourable result.

CASE 10

C.B., a white man, aged 44 years, was first seen because of two small gummatous lesions of the skin and a mild syphilitic periostitis of the left ulna. His previous health had been good and there was no history of syphilis. The physical examination revealed a soft systolic murmur heard best at the right cardiac base, a very slight accentuation of the aortic second sound, and a very questionable increase in the supracardiac dullness, which was not confirmed by x-ray. There was no evidence of arteriosclerosis or hypertension. The blood Wassermann reaction was positive and the cerebrospinal fluid examination was negative. He was seen by two cardiologists, who were unable to make a diagnosis of aortitis. Despite the indefiniteness of the cardiac findings he was given preliminary treatment with mercury, followed by six months' treatment with bismuth salicylate. Treatment with neosalvarsan was then cautiously begun. Indefinite bronchial symptoms began after the third injection; a sense of constriction was noted after the sixth treatment, while after the 7th injection, 0.3 grams, he developed a myocardial infarction, and a pericardial friction rub, with electrocardiographic evidence of coronary involvement. The patient was hospitalized for three months and made an uneventful recovery. He has been followed for three years, during which time intermittent treatment with bismuth has been given, and no further complications have developed, although the signs at the right cardiac base have become accentuated.

This patient illustrates *par excellence* the difficulty in establishing the presence of early syphilitic aortitis. Only in the presence of fairly extensive damage will the fluoroscope reveal evidence of aortic dilatation or auscultation disclose the diastolic murmur of aortic regurgitation. In the presence of syphilis more significance should be placed on such vague and indefinite findings if early diagnosis is to be made. The myocardial infarction, plus the subsequent development of the paradoxical increase in physical signs was highly suggestive of cardio-aortic syphilis. Its relatively early development was unusual, and should not be construed as a contraindication to arsenical therapy in early cardiovascular syphilis. The recent work of Cole^{5, 6} and his co-authors has established the value of such treatment, after careful preparation, if syphilitic involvement of the myocardium or of the coronary arteries can be excluded.

After the onset of clinical latency a negative spinal fluid examination practically insures the patient against neural axis involvement.⁵ In

sharp contrast is the situation obtaining in cardiovascular syphilis in which the blood Wassermann reaction, though usually positive, may not only reflect such changes but may be an indication of other visceral syphilis when specific cardiovascular involvement is not present. The blood Wassermann reaction may also remain positive in the absence of potentially damaging visceral lesions, and when the character of the disease approaches that of true permanent latency. On the other hand, serious cardiovascular involvement may develop even though the blood Wassermann reaction remains persistently negative. The inadequacy of clinical examination in the early diagnosis of cardiovascular syphilis and the frequent asymptomatic nature of the process⁷ renders imperative a high index of suspicion for the insignificant beginnings of such involvement on the one hand, and on the other a thorough course of treatment in every patient in whom the syphilitic infection is comparatively recent.

COMMENT

The present paper serves to focus attention upon many indefinite or subclinical syndromes encountered in syphilis, and to emphasize that active pathological changes are an integral part of latent syphilis. After the initial period of invasion an imperfect form of cellular (and humoral?) immunity is developed. Spirochaetes, with the exception of those in inaccessible areas or in a relatively non-reactive tissue, are rapidly destroyed, while those remaining provoke a low-grade tissue reactivity. This low-grade activity, unless it occurs in a particularly vital region, constitutes clinical latency, and includes approximately one-third of all patients with syphilis. During the course of years this activity may become lessened and the latent phase become permanent. In a second group bodily structures, vital and otherwise, are slowly transformed into replacement tissue by the syphilitic inflammatory foci. In a third group an extensive or explosive tissue reactivity may develop, depending on hyperallergy or a local lowering of resistance, with resultant acute clinical manifestations. The rapidity of onset, the definiteness and the course of the clinical manifestations will depend not only on the above factors but also on the site of the diseased process. In the liver, for example, a relatively large amount of tissue destruction (unless an important duct or vessel

is involved) will occur before symptoms appear. Similarly, in the pancreas or the pituitary gland destruction must be extensive before symptoms ensue. On the other hand, cerebrovascular accidents usually occur with devastating suddenness in an apparently latent or normal situation, due to the relatively small amount of diseased tissue necessary to precipitate the thrombotic or hæmorrhagic accident.

In many of these instances the insidious nature of the pathological process results in the development of obscure syndromes which may not appear directly referable to syphilis. Frequently, only the most painstaking history, the consideration of apparently non-syphilitic entities on a possible syphilitic basis, prolonged personal observation, and the careful interpretation of the response to the therapeutic test will verify the syphilitic nature of the process. Yet despite every precaution the diagnosis is often confirmed only by the development of some tragic, unsuspected complication, or by the evidence revealed at the autopsy table.

The minimum requirements for a diagnosis of latency are a negative physical examination, a normal cerebrospinal fluid and normal fluoroscopic findings. In the residual group the diagnosis will be established by the elimination

of other causes and by a careful interpretation of the presenting symptoms and of the response to the therapeutic test. It should be recalled that of all those in whom a diagnosis of latent syphilis is made fully 30 per cent will develop signs of subsequent activity, of which approximately one-half are specifically referable to the cardiovascular system. Spontaneous cure occurs in about 35 per cent, while another 25 to 35 per cent remain clinically inactive, but show a positive blood Wassermann reaction. The need for a thorough investigation and treatment in all persons in whom the disease is comparatively recent is obvious, if irreparable damage is to be avoided.

REFERENCES

1. O'LEARY, P. A.: Latent syphilis and its treatment, *Med. Clin. N. Am.*, 1937, 21: 882.
2. WARTHIN, A. S.: The lesions of latent syphilis, *Proc. Staff Meet. Mayo Clinic*, 1930, 5: 200.
3. WILE, U. J.: Occult syphilis: a neglected factor in diagnosis and treatment, *Wisconsin M. J.*, 1933, 32: 673.
4. MCLESTER, J.: The influence of syphilis on the course of other diseases, *Ann. Int. Med.*, 1928, 2: 348.
5. MOORE, J. E., COLE, H. N., O'LEARY, P. A., STOKES, J. H., WILE, U. J., for the Cooperating Clinics, and CLARK, T., PARRON, T., USILTON, L., for the United States Public Health Service: Cooperative clinical studies in the treatment of syphilis: latent syphilis, *Veneral Disease Information*, 1932, 13: 317, 351, 371, 389 and 407; *idem*: 1933, 14: 1.
6. COLE, H. N., with USILTON, L. and MOORE, J. E., O'LEARY, P. A., STOKES, J. H., WILE, U. J., PARRON, T., VONDERLEHR, R. A.: Cooperative clinical studies in the treatment of syphilis: cardiovascular syphilis, *Veneral Disease Information*, 1936, 17: 91.
7. WILE, U. J. and SNOW, J. S.: Occult cardiovascular syphilis, *Am. J. M. Sc.*, 1938, 195: 240.

THE ACUTE GALL BLADDER: EARLY VERSUS LATE OPERATION*

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THE most controversial topic in connection with biliary surgery today is the management of the "acute gall bladder". Surgeons of outstanding ability are divided in their opinion as to whether it is best to operate on these cases immediately or after the acute attack has subsided. Walton,¹ in 1923, was one of the first to advocate early operation to prevent gangrene, and also because he considered removal more easily accomplished in the early oedematous stage than later. But, we have many equally well known surgeons who emphatically state that operation during the acute stage entails unwarranted risk, and that cholecystectomy is definitely more difficult and more

hazardous in the early stage than after the oedema has subsided. A questionnaire directed to the teachers of surgery in the seven Canadian medical schools states that the delayed treatment is practised by the majority and is taught as the method of choice. There is some confusion regarding the exact meaning of "early operation", whether early after the beginning of the attack or after admission to hospital is not clearly defined by some writers. It would appear that many who oppose early operation base their conclusion on their experience in dealing with cases that have been ill on an average of five days, as the records in large teaching hospitals show this to be the average length of time that these patients have been sick before admission.

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It is not the purpose of this paper to enlarge upon criteria to decide when to operate on late cases of acute cholecystitis. In my opinion, the opportune time has passed at the end of five days. Many will have developed dangerous complications such as gangrene, perforation or pericystic abscess; all will have seriously disturbed metabolism and chemistry as the result of starvation and dehydration, and they will require days or weeks of treatment with glucose and saline to restore this imbalance to a safe state when an elective operation can be performed. One will, however, often be forced to do a life-saving operation of drainage, as these complications often do not subside, but steadily get worse. Diabetes and cardiovascular disease are associated with these late cases of biliary disease in a high percentage of cases, and must always be carefully investigated before any surgical procedure is undertaken.

The purpose of this paper is to present a brief summary of the literature on the topic of acute cholecystitis that has accumulated within the past few years. The vast majority of these papers are written by those who advocate early operation and produce statistics to support their belief in the superiority of this method over the old. I also wish to present my personal experience with 41 cases of acute cholecystitis.

One objection raised by those who advocate delay is the danger of spreading infection, if these cases are operated on in the acute stage. This fear is based on the assumption that infection is the exciting and primary etiological factor producing the "acute gall bladder". But, most students of pathology now agree that obstruction of the cystic duct is the primary factor, and infection, when present, is almost always secondary and depends on obstruction for its development. Andrews² found many cultures from these early obstructed gall bladders to be sterile. Denton³ also found infection to be secondary to obstruction, and it did not appear until several days after obstruction had occurred. Wilkie⁴ could produce acute cholecystitis in animals by injecting streptococci intravenously only after the cystic duct had been obstructed. Drennan,⁵ of the Mayo Clinic, found 81 of 100 acute gall bladders to be sterile.

The cystic duct has been found to be obstructed in all cases of acute cholecystitis; 95

per cent were obstructed by a stone. Denton's³ work on these early lesions shows that when a stone becomes impacted the wall of the cystic duct adjacent to the stone becomes swollen and oedematous. This oedema soon extends to the periductal tissues and obstructs the veins and lymphatics leaving the gall bladder, which are in close approximation to the tortuous cystic duct. Branches of the cystic artery, especially in the aged, are often thrombosed, causing actual infarction in the wall of the viscus. Venous and lymphatic obstruction soon causes oedema in the wall of the gall bladder.

When the cystic duct is occluded, bile neither enters nor leaves the gall bladder. The bile that is present when obstruction occurs soon becomes absorbed, but the mucous membrane continues to secrete and the gall bladder becomes tensely distended with mucus or "white bile". Two factors favour infection when this obtains: (1) stagnation, and (2) the absence of the bactericidal effect of fresh bile.

It is argued that perforation is rare, and unlikely to cause general peritonitis, and that there is not the same urgency for early operation as in appendicitis, but statistics show that it occurs much more often than is generally known. Taylor⁶ reported an incidence of 11.5 per cent of his cases ruptured, 60 per cent were walled off; 40 per cent had ruptured into the free peritoneal cavity. His earliest case of perforation was on the third day after the beginning of the attack. Judd⁷ reported 61 cases of ruptured gall bladders; the patients had been sick on an average of 20 days. Heuer⁸ found 25 per cent of his series gangrenous at operation.

The policy of waiting for an acute gall bladder to "cool off" is an extremely dangerous one, because there are no reliable criteria to enable the most astute clinician to say that this case is improving, or that case is developing dangerous complications. The leukocyte count is held by some as the most reliable single sign, and is usually over 15,000 when gangrene is present, but it has been found many times to steadily decrease in cases that were developing pericystic abscess and eventually went on to perforation. Mentzer⁹ reported 4 patients with ruptured gall bladders in a teaching hospital that were observed for many days and eventually died without the diagnosis being made until autopsy. He also reported 11 other

ruptured gall bladders that had been under observation from 5 to 19 days before operation. Judd⁷ reported 7 ruptured cases where the diagnosis was so obscure that it was not made until autopsy was performed.

It has been argued that the great majority of these patients get well at home on medical treatment, and if one operated on every case of gall-stone colic you are virtually preventing acute cholecystitis, not curing it. McKenty¹⁰ reported the results of medical treatment of 401 cases; 69 did not improve, 24 rapidly became worse, and 16 died, *i.e.*, 109, or 27 per cent, of 401 cases failed to get well on medical treatment. Zinninger¹¹ and Taylor⁶ in two separate series reported that 63 per cent of their cases failed to improve or became worse on expectant treatment; only 37 per cent improved. If gall-stone colic is mistakenly operated on for acute cholecystitis it is not a very serious mistake, since both the catastrophies and the poor results of operations on the gall bladder are due, in large part, to delay in the institution of surgery. There would seem, therefore, to be no logic or reason for the prolonged non-surgical treatment of cholecystic disease, especially when symptom-producing stones are present.

I have found that if the acutely distended gall bladder is deflated by aspiration and removed from the fundus downwards, the unorganized oedematous tissue permits removal in the early stage with relative ease, and by this method the cystic duct and artery can be safely separated from the oedematous tissues that obscure the anatomy of that region. Walton,¹ as I have mentioned earlier, gave this as one reason for advocating early operation. Zinninger¹¹ states: "In the early oedematous stage the gall bladder shells out relatively easily, whereas by the time the patient has 'cooled off', organization in the still red, thickened viscus may have progressed sufficiently to render dissection considerably more difficult." Clute¹² also had the same experience and states: "In our experience the delayed operation of cholecystectomy is definitely harder than the early one." However, the operation which may be ideal from the standpoint of ultimate morbidity may have to be modified for the sake of immediate mortality. Cholecystectomy, as will be shown later, is a better operation than cholecystostomy, but the latter may frequently be safer and more prudent in

many cases. No one would think that a deeply situated, inaccessible, acutely inflamed gall bladder should be removed from an extremely sick person.

The real point at issue, however, is which procedure is going to result in the lowest mortality and least morbidity with the best hopes of permanent cure. Zollinger¹³ reported 235 cases treated conservatively with a mortality of 10.4 per cent; R. R. Graham¹⁴ reported a mortality of 7.7 per cent treated conservatively; Pratt,¹⁵ Zinninger,¹¹ McKenty¹⁰ and Graham and Hoefle¹⁶ reported 69 cases that were operated on within 48 hours of the onset with only one death, a mortality of 1.4 per cent. These authors reported 167 cases operated on within 48 hours with a mortality of 3.5 per cent. Taylor⁶ placed the mortality at 5 per cent if operation is done within the first 4 days. After 4 days the mortality increases to 24 per cent. Zinninger¹¹ had no mortality when the operation was done during the first 48 hours; if done between the 2nd and 5th day the mortality was 6.6 per cent; after 5 days, 25 per cent.

The economic aspect of an operation cannot be entirely ignored in these days of depression and expensive hospitalization. Patients on delayed treatment are sick on an average of 5 days at home, and Graham¹⁴ states that his patients were treated on an average of 12 days in hospital before operation. It has been reported by many writers that cholecystectomy can be done in a much higher percentage of cases in the early stages, and a much shorter period of hospitalization is necessary after cholecystectomy than after drainage. Kunath's¹⁷ cases of cholecystectomy remained in hospital on an average of 17 days; cholecystostomy cases remained 9 days longer, or 26 days; and only 40 per cent get complete relief from symptoms after drainage and many require another operation.

My personal experience is based on 41 cases of acutely obstructed gall bladders treated within the past 10 years, selected from 327 cases of gall bladder disease which required surgical therapy. The diagnosis was made on the signs and symptoms of acute inflammation, pain, elevated temperature, pulse and white blood count, with tenderness and spasm over the gall bladder. At operation the gall bladder was found to be swollen, oedematous and tensely distended; the cystic duct was occluded in all cases but two by

a stone—94.6 per cent. The contents of the gall bladder consisted of one or more stones, except in two cases. Bile was present in the early cases, but as the period of time increased after the obstruction the amount of bile became less and less and was found mixed with mucus and pus. The diagnosis was confirmed pathologically in all cases where the viscus was removed. The early cases showed oedema of the wall; as time elapsed suppuration and gangrene were found. The earliest case of gangrene was in a man 75 years of age who was operated on within 24 hours after the first pain; here a gangrenous infarct was found, involving about one-third of the wall. Eight cases of gangrene were found in the group operated on within 48 hours.

The ages ranged from 17 to 79 years; the average age was 50 years. There were 7 patients over 70 years, only one of whom had cholecystectomy. He had had a cholecystostomy 10 years previously and was considered too old then to have cholecystectomy. He was operated on within 48 hours, made an uneventful recovery, and left the hospital on the 17th day, 8 days sooner than he did when he had his gall bladder drained 10 years before.

Thirty-nine of these 41 patients were operated on; 21 within the first 48 hours after the attack began; the other 18 had been sick on an average of 5.5 days. These late cases were much sicker and required a much longer period of treatment before operation than the early ones. Cholecystectomy was possible in 61 per cent of the early cases, but only possible in 22 per cent of the late cases. There were no complications in the early cases, but a ruptured gall bladder was encountered in 7.6 per cent of the late group. These patients who had ruptured had been ill on an average of 8 days. Acute pancreatitis was present in 3 late cases; all recovered, but one died two months after leaving the hospital with another attack of pancreatitis.

All patients who had cholecystectomy have remained well, but 3 patients returned within one year after cholecystostomy to have the gall bladder removed, and 4 others are having troublesome symptoms. This has been the experience of many writers. The Mayo Clinic reported 84 per cent cures after cholecystectomy. Pratt¹⁵ reported that 18 per cent of his cases returned for second operation within one year after drainage. The average length of stay in hospital after cholecystectomy was 14.7,

or practically one week less than after drainage, which was 21.7 days.

There was only one death in this series and that was of a physician who was ill 5 days before admission to hospital, and, after consultation with two other surgeons, operation was deferred for 7 weeks, when the temperature, pulse, and leukocyte count were normal. However, at operation, the gall bladder was found to be necrotic and filled with pus and stones. He died on the table, a mortality of 2.5 per cent, or 1 death in 39 cases.

From a review of the literature and my own experience, I am convinced, both from the experimental and clinical evidence, that the primary pathological lesion in the "acute gall bladder" is not a septic process but an interference with the blood supply to an intraperitoneal viscus, caused mechanically in 95 per cent of cases by a stone impacted in the cystic duct. If this obstruction is relieved before infection sets in the mortality can be reduced from the present appalling figure to practically the vanishing point; a higher percentage of complete cures can be assured if operation is done early because it has been shown that cholecystectomy can be done much more often in the early stage than later. Less suffering before the operation can be promised and at least one week less stay in hospital after a cholecystectomy than after drainage.

Some who advocate delayed operation admit that if they had the opportunity of seeing these cases earlier they would probably operate on them sooner, but how can they expect to accomplish this if they continue to teach that delayed is better than immediate operation? I see no hope of any change until there is a change in the teaching. If the general practitioner does not call for a surgical consultant for five days, it would appear to be due to present-day teaching. Of course the decision regarding the optimal time of operation has to be made after considering the general condition of each patient individually, but it has been my experience that in patients with an acutely obstructed gall bladder for two days or more the symptoms will not, as a rule, subside completely under any treatment except surgery. Hence, further delay is dangerous and useless.

SUMMARY

Infection is not the basic cause of acute cholecystitis, but obstruction to the ducts and

blood supply, which produces oedema, infarction and gangrene. The longer this process continues, the more chance there is for infection and its complications to develop. If this obstruction is interrupted by cholecystectomy within the first three days infection rarely occurs, complications are few, and the final results are very satisfactory.

REFERENCES

1. WALTON, A. J.: A Textbook of the Surgical Dyspepsias, Longmans, London, 1923, p. 512.
2. ANDREWS, E.: Detailed studies of a series of gall-bladder cases, *Surg., Gyn. & Obst.*, 1933, 57: 36.
3. DENTON, J.: The mode of origin of gall-bladder lesions, *Arch. Surg.*, 1927, 14: 1.
4. WILKIE, A. L.: The bacteriology of cholecystitis, *Brit. J. Surg.*, 1928, 15: 450.
5. DRENNAN, J. C.: A bacteriologic study of the fluid contents of 100 gall bladders removed at operation, *Ann. Surg.*, 1922, 76: 482.
6. TAYLOR, F.: The acute gall bladder, *Surg., Gyn. & Obst.*, 1936, 63: 298.
7. JUDD, E. S. AND PHILLIPS, J. R.: Acute cholecystic disease, *Ann. Surg.*, 1933, 98: 771.
8. HEUER, G. J.: The surgical aspects of acute cholecystitis, *Ann. Surg.*, 1937, 105: 758.
9. MENTZER, S. H.: Obstructive cholecystitis, *Surg., Gyn. & Obst.*, 1936, 62: 879.
10. MCKENTY, J.: Acute cholecystitis, *Canad. M. Ass. J.*, 1938, 38: 236.
11. ZINNINGER, M. M.: The surgical treatment of acute cholecystitis, *Ann. Surg.*, 1938, 107: 543.
12. CLUTE, H. M.: Immediate versus delayed surgery in acute cholecystitis, *Surg., Gyn. & Obst.*, 1938, 66: 122.
13. ZOLLINGER, R. AND BRANCH, C. D.: Acute cholecystitis; a study of conservative treatment, *New Eng. J. Med.*, 1936, 245: 1173.
14. GRAHAM, R. R.: The diagnosis and management of acute cholecystitis, *Canad. M. Ass. J.*, 1935, 32: 283.
15. PRATT, G. H.: Cholecystectomy and cholecystostomy in acute suppurative and gangrenous cholecystitis, *Am. J. Surg.*, 1933, 27: 46.
16. GRAHAM, H. F. AND HOEFLE, M. E.: Acute cholecystitis; the results of operation within 48 hours of onset of symptoms, *Ann. Surg.*, 1938, 108: 874.
17. KUNATH, C. A.: The treatment of acute cholecystitic disease, *Surg., Gyn. & Obst.*, 1937, 65: 79.

ACUTE HÆMATOGENOUS OSTEOMYELITIS*

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DURING the past several years a great amount of literature has accumulated on the subject of acute osteomyelitis both as regards its etiology and its treatment. A review of this shows that many of the writers fail to stress sufficiently both components of this disease, namely, the general bacterial infection as well as the local lesion in the bone tissue. These two elements must be kept in mind because treatment and prognosis will vary according to which of the two components is more prominent in any particular case.

Orr¹ has advanced a method of surgical drainage of the lesion in bone tissue followed by the placing of the part at rest by means of plaster casts. Both his results and those of many other surgeons amply confirm the value of this form of treatment (see especially Hobart and Miller²). So that to a great extent it is gradually replacing other procedures as the one of choice. Many today feel that this alone is the treatment of the disease. Wilensky,³ although laying great stress on both components of the disease, points out that in many cases the bone lesion is of far less importance and that these cases do not need immediate surgical interference as has previously been the accepted view.

In all probability a middle path between these

two extremes is a sound method of treatment, having due regard to both the local lesion in the bone as well as the general bacterial invasion, paying particular attention to the one more dominant, but not forgetting that the other must be dealt with. It is with this in mind that the following series of cases is presented. Although numerically small, it represents, the writers feel, a fairly typical collection both as to the manifestations of the disease as well as treatment and result.

The cases in this series had as the etiological agent either the *Staph. pyogenes* or the *S. hæmolyticus*. The type of treatment for the local condition in the bone has varied from simple incision and drainage of the soft tissue abscess, to more radical opening of the bone, followed by various irrigations, diaphysectomy, and, finally, the treatment as outlined by Orr. In reviewing these cases, it is found that they can be put into two large groups on the basis of the blood culture being positive or not. The group of those with positive blood culture is possible of subdivision on the basis of the number of colonies per c.c. of blood, whether this was high or low. Therefore, the cases can be arranged in the following three main groups.

GROUP I.

In this group are placed those cases of acute osteomyelitis of one or more of the long bones which did not show positive blood culture on or

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shortly after admission to hospital. Under this heading are placed 5 cases of this series. In all five the offending organism was *Staph. pyogenes*, which was grown from the pus found in the bone at operation. The onset in each case was rather sudden, and in two of them, according to the history obtained from the parents, followed, at least in time, trauma of a greater or lesser degree. The length of time elapsing between the onset of the symptoms and admission to hospital varied from 24 hours to 4 days, the average being 48 hours.

The general condition of the different patients showed considerable variation in severity, from mild constitutional upsets with slight elevation of temperature, leucocytosis and increase in the pulse rate, to more serious disturbances with hyperpyrexia and delirium.

Three of the cases were treated by the method of Orr,¹ one was treated by opening the bone widely, frequent packing of the wound with paraffin gauze and the use of picric acid irrigations, followed by calcium carbonate spray. The remaining one was treated in a conservative fashion, with aspiration of the soft tissue abscesses and blood transfusions, followed in about two months' time by sequestrectomy of the left femur and diaphysectomy of the right radius. The results show that those treated by the method of Orr have had no recurrence of the disease, and that, once healed, the wound has shown no tendency to sinus formation. The other two patients have had a long convalescence over a period of at least two years, the condition having become chronic.

GROUP II.

In this group are placed those cases of acute osteomyelitis of the long bones which showed only a slight growth of organisms from the blood stream shortly after admission to hospital. For purposes of grouping this heading applies to those cases having a maximum growth of not more than 8 colonies per c.c. of blood.

Two cases of this series can be placed under this heading. Again the organism isolated from the pus in the bone at operation was the *Staph. pyogenes*. The onset in these cases was sudden, one following very closely on an attack of furunculosis, the other shortly after an acutely inflamed throat, which, it is interesting to note, in association with swelling of one ankle led to a primary diagnosis of acute rheumatic fever. Both these cases were admitted to hospital with-

in two days after the onset of symptoms. Both children were acutely ill, their temperature ranging from 104 to 105° with a rapid pulse and a marked leucocytosis.

One patient was treated shortly after admission by the Orr method, the other was kept on the medical service for two days, after which the child was transferred to the Department of Surgery. Following this, routine treatment was carried out after the method of Orr. The blood culture taken shortly after admission was later reported to be positive; however no attempt was made to treat the blood stream infection specifically because by the time the bacteriological report was made the child's condition had improved to such an extent that it was evident the blood was rapidly becoming or had become sterile. These children have been discharged from the hospital, and at the present time one is able to be up and about, but unfortunately has an obliteration of the ankle joint due to the secondary septic arthritis that was present at the time of admission. The other after seven months' stay at the hospital was discharged with the leg still incased in plaster. The wound is almost completely healed and x-ray examination of the bone showed regeneration to be satisfactory.

GROUP III.

In this group are placed all those cases of acute osteomyelitis of the long bones which showed a marked growth of organisms in blood taken shortly after admission to hospital. In this group are placed those showing a culture exceeding 8 colonies per c.c.

This group can again be divided according as to whether the offending organism was (a) *S. hæmolyticus* or (b) *Staph. pyogenes*. Of the eleven cases under this heading, three are placed in the subdivision (a).

CASE 1

The first case, in a male child, was one which began very acutely with headache, fever and pain in the right arm. There was no history of trauma or recent infection of any kind. The following day he was admitted to the hospital, temperature 106°; pulse 150. Blood culture taken prior to operation was reported two days later as positive. Treatment consisted in surgical drainage of the humerus as outlined by Orr, the arm being held in a Thomas splint. Operation did not affect the temperature in any marked degree. The patient continued a course progressively downhill, evidences of secondary foci appeared, the child developed toxic jaundice, albuminuria, fluid in the chest with evidences of a pneumonic process in both lungs. Four days after admission 50 c.c. of Burroughs and Wellcome anti-streptococcal serum were given. There was no effect on the temperature or on the general condition of the patient.

Despite repeated blood transfusions, the number of colonies per c.c. of blood continued to rise and 10 days after admission had reached 150. The patient died 13 days after admission.

The other two cases in this group followed on the heels of a severe upper respiratory infection, the signs and symptoms referable to the bone lesion developing about two to three weeks after the onset of the upper respiratory infection.

CASE 2

The first of these cases was admitted to the hospital, April, 1933; the child was taken ill 10 days previously with a rather high temperature and was quite restless. Inside of two days a definite cervical adenitis had developed, which was followed in two days' time by the formation of a retro-pharyngeal abscess. On the fourth day of the illness this abscess was opened. Temperature still continued to run a hectic course. Then an erythematous patch which increased in size quite rapidly developed on the dorsum of the left hand. On the day prior to admission the swelling of the hand was spreading so rapidly and the child's condition was so critical that admission to hospital was advised. After 24 hours in hospital a diagnosis of septic scarlet fever was made. The swelling on the dorsum of the hand was incised and the wound held open with gauze packing. By this time, a report on the blood culture showed that there were 10 or more colonies per c.c. This condition was treated by means of several blood transfusions. Two weeks later the wound on the back of the hand still continued to discharge. X-ray examination showed that there was definite evidence of bone destruction in the lower end of the right radius, but no sequestrum formation. Therefore the child was allowed to continue with frequent changes of packs, and inside of 6 weeks' time was in suitable condition to be discharged. Following this, the lesion in the bone healed well without the necessity of any further surgical intervention.

At present the child is well, there is no limitation of movement at the wrist joint, and the lesion in the bone is well healed. There has never been any recurrence of the swelling in the arm or hand.

CASE 3

The second child in this group had been ill at home for about two weeks, refused feedings, and suffered from a cold which had appeared to have cleared up by time of admission to hospital. Four days prior to admission it was noticed that the child's left leg just above the knee was reddened and slightly swollen and the child cried if this area was touched. The swelling and redness increased so rapidly and the child's general condition became so bad that the parents brought him into hospital. On admission the temperature was 104°, the child appeared acutely ill, had a red throat and a mild otitis media. Locally there was all the evidence of an inflammatory lesion of the left femur. This was treated soon after admission by the Orr method. Blood culture taken on admission showed a large number of colonies of *S. hæmolyticus* per c.c. Therefore the child was given frequent blood transfusions and large doses of sulfanilamide. Two days later both drums were opened. The temperature still remained elevated. Then the child developed osteomyelitis of the left humerus. This in turn was followed by suppurative parotitis, followed by an osteomyelitis of the right humerus. As these new lesions appeared they were opened and treated by the same method. Blood culture, repeated one week after admission, was negative as were all the subsequent ones. Following treatment of the right humerus the child's temperature gradually fell and the general condition improved rapidly.

At the end of 4½ months he was able to be discharged, all the wounds being well healed, and all joints freely movable, with no evidence of any recurrence.

Subdivision (b) is represented by those cases that showed a very marked staphylococcal septicæmia at the time of admission. There were 8 in number. These children were all extremely ill on admission and had been so on an average of about 3½ days before admission to hospital, with one exception, that being kept outside for almost 6 days.

In 3 of the cases there was a definite history of trauma; in one other there was a history of an acute tonsillitis a few days before the onset of pain in the bone. The remaining 4 had no previous history of any infection or injury. The temperatures on admission ranged from 100.3 to 105°. In all cases recourse was had to immediate surgical intervention. In 5 cases the tibia was involved, completely in one case, in the upper portion in three, and the lower third with involvement of the ankle in the remaining one. The remaining three cases represented a lesion of the upper end of the humerus and two in the lower end of the femur, respectively. Blood cultures taken shortly after admission showed 50 or more colonies per c.c. of blood. The type of surgical treatment varied in the different cases. Five were treated by the Orr method; one by diaphysectomy of the tibia; two by drainage and repeated changing of packing.

All cases were treated with staphylococcus antitoxin and in only two of the cases was any effect noted on the septicæmia.

Two of the cases will be taken up in detail.

CASE 4

A boy, 9 years of age, was brought to the hospital in January, 1933, four days after a slight injury to the left leg. The day after his injury his knee was swollen and there was considerable pain in the tibia just below the knee joint. Three days later the child became so ill that a doctor was called and immediate admission to the hospital was advised. It can be seen from Chart 1 that the temperature on admission was 105.3°. The child was delirious and blood culture showed 20 colonies per c.c. There was a definite osteomyelitis of the tibia, plus a septic arthritis of the left knee joint. On the day following admission the leg was opened and a small opening was made in the osteomyelitis cavity. As can be seen from Chart 1, there was little or no influence on the temperature, and the second blood culture taken three days after admission to hospital was still positive for the *Staph. pyogenes*. Following reports of others the use of bacteriophage and charcoal intravenously was advised. Treatment was started on the fifth day after admission to hospital; 2 c.c. of a 2 per cent emulsion of charcoal and 1.5 c.c. of bacteriophage were given intravenously on five successive days. The temperature still continued high. The child's condition was only fair, and the blood culture still remained positive, although the number of colonies per c.c. had diminished somewhat. It was therefore decided to make use of staphylococcus antitoxin as prepared by the Connaught Laboratories, intravenously. Administration of this serum was accomplished by diluting 10 c.c. of the serum in 10 c.c. of normal saline, and giving this every hour

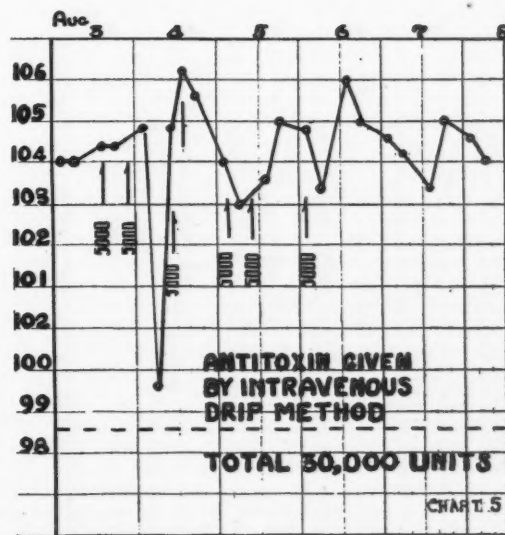
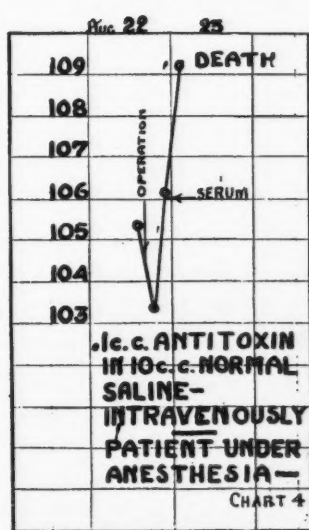
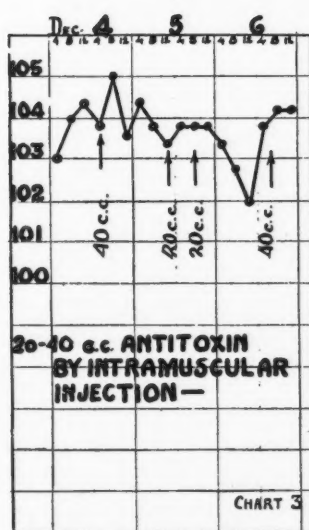
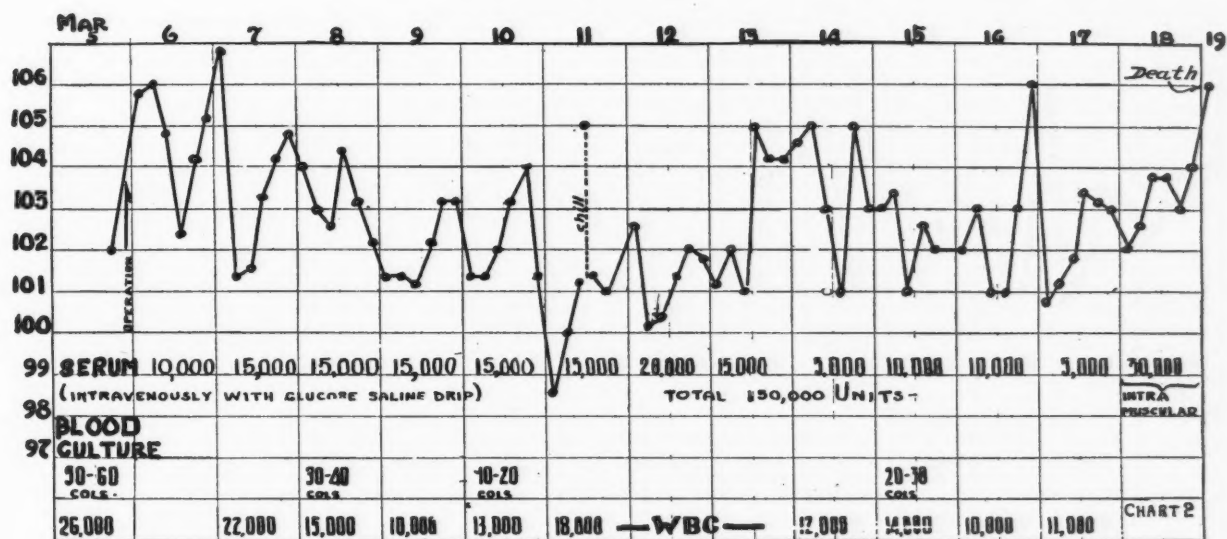
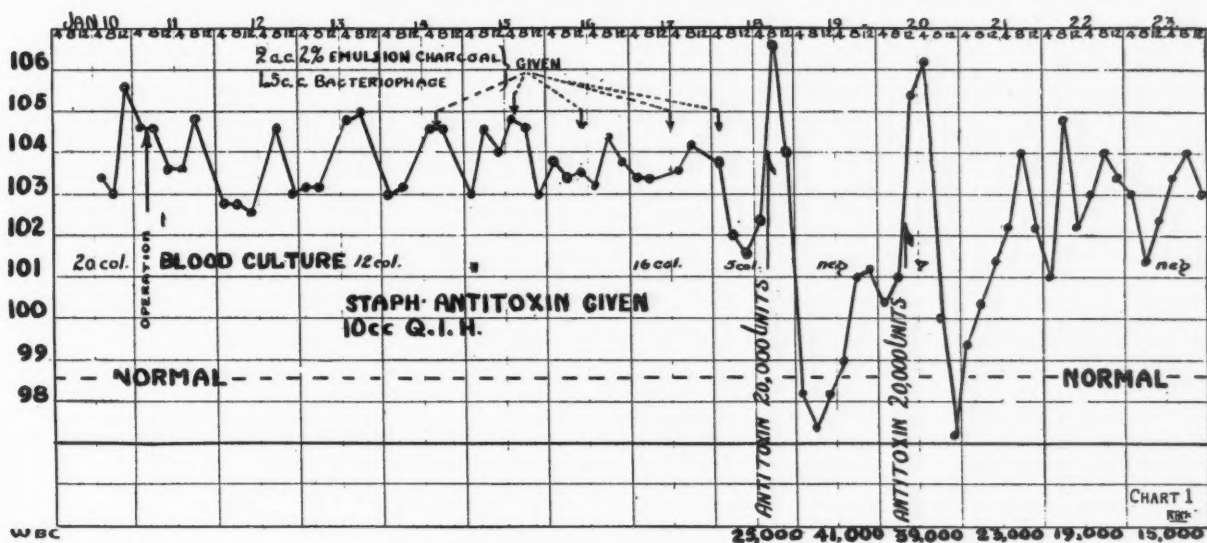


Chart 1.—This shows a case treated with minimal surgical intervention, plus attempts to control the bacterial invasion. Note also the reaction to staphylococcus antitoxin on two occasions. Chart 2.—This shows a case under heading Group III (b). Treated by Orr method plus staphylococcus antitoxin. Note the lack of reaction to the serum when given in connection with the intravenous drip. Chart 3.—This shows the lack of reaction when serum is given by the intramuscular route. Chart 4.—This shows an extreme reaction developing after injection intravenously of a small amount of antitoxin. While this is the extreme form of reaction it is not too uncommon (see also Chart 1). Chart 5.—To show lack of reaction following administration of antitoxin in association with continuous intravenous therapy (see also Chart 2).

until 5 injections had been made. As can be seen again from the chart the systemic reaction to the injection was marked. Blood culture taken following this showed a diminution in the number of colonies. Forty-eight hours after the first course of serum a second was begun. Once again a severe systemic reaction took place, but the blood culture became negative for the first time since admission. The temperature continued to run between 101 and 104° and was of the septic type. The general condition continued to improve in spite of the temperature elevation and pulse rate. A blood titre was done at the end of three weeks and was found to be low. A course of staphylococcus toxoid was begun. At the end of the second month in hospital the blood titre determination showed that a high level had been reached. As time went on patient developed destructive processes in both hip joints. One year later he developed osteomyelitis in one humerus. During the years 1935-36 he had several flare-ups in the old sites, and was only able to be discharged from the hospital late in 1936, when for the first time the sinuses were dry. He was extremely crippled, both hips and one knee being completely fused. He was seen from time to time in the out-patient department and showed occasional soft tissue abscesses. Suddenly in August, 1937, he had an acute flare-up in the left femur and was brought to the hospital extremely ill, delirious and with a temperature of 104°. The left femur was exposed, drained, packed and plaster applied. Blood culture was markedly positive. Staphylococcus antitoxin was given by the intravenous drip method. Blood culture showed a continual rise in the number of colonies, multiple secondary abscesses formed in the lungs, and death occurred 9 days after admission.

It is interesting to note that in his second admission the white blood cell count at no time rose above 10,000, while on the previous admission, there was a rise to about 40,000 during the acute stage of the disease.

CASE 5

Girl, 12 years of age, admitted with a history of an upper respiratory infection followed by nausea, vomiting and some abdominal pain two weeks prior to admission. Pain over the region of the right knee developed 4 days before entrance into hospital. On the following day, redness, swelling and tenderness were noted below the right knee joint. On closer questioning a history of slight injury one week before the onset of the pain was elicited. Examination on admission revealed definite evidence of osteomyelitis at the upper end of the right tibia. Blood culture was markedly positive for *Staph. pyogenes*. Following the surgical treatment of the local lesion in the bone the temperature continued elevated for two days, then it began to fall, and on the fifth day after admission the child's general condition was somewhat improved, and blood culture showed the number of colonies to have fallen appreciably. However, on the sixth day the child suffered a chill and definite evidence of a pneumonic process was made out in the chest. From this time, the temperature continued to rise and on the 14th day after admission death occurred. An attempt was made in this case to combat the septicæmia by means of serum, and large doses, approximately 15,000 units, were given each day intravenously, using the drip method. Once again, this did not prevent the occurrence of secondary abscess formation, although for the first few days some of the toxic manifestations of the disease were lessened (see Chart 2).

The other cases of this group followed much the same course, and the results of treatments were very discouraging.

SUMMARY OF TREATMENT

Orr treatment—13 cases. Five cases were accompanied by severe staphylococcus septicæmia; all died. One case was accompanied by severe streptococcus septicæmia; died. One case was accompanied by severe streptococcus septicæmia; recovered. (Followed by development of two other foci). Six remaining cases in which this treatment was used are all well. The wounds are dry and there are no further recurrences.

Diaphysectomy—2 cases. One with marked staphylococcus septicæmia, died. One with marked staphylococcus septicæmia recovered. (Numerous recurrences in different bones; a considerable amount of plastic work was necessary over a period of four years before the child was able to be up and about).

Minimal drainage with packing frequently changed—3 cases. One associated with severe staphylococcus septicæmia recovered. (He had a long convalescence, numerous recurrences and formation of new foci). One with streptococcus septicæmia recovered. One with a negative blood culture recovered. (Patient had long convalescence over a period of two years, and considerable tendency to recurrences).

Conservative (aspiration of soft tissue or sub-periosteal abscess)—1 case. With negative blood culture, recovered. (Four months of conservative treatment followed by diaphysectomy).

TABULATION OF TREATMENT AS TO CASES

Group I (those with negative blood culture)—5 cases. Three were treated by Orr method. Stay in hospital averaged about 5 to 6 months. All well at the present time. One was treated by drainage and frequent change of packings. (No fixation of the limb by casts). Case in hospital for almost one year, came back to hospital two years later with chronic sinuses and was then treated by Orr method. No further trouble. One was treated conservatively (aspiration of soft tissue abscesses). Had to have diaphysectomy four months later. Much deformity and numerous readmissions for flare ups of the chronic condition.

Group II (those with only slightly positive blood culture)—3 cases. All treated by Orr method. All cases are well at the present time. One has stiff ankle, one has changes in knee and is still in plaster. One has changes in hip joint. He gets about with a walking caliper.

Group III (those with markedly positive blood culture)—10 cases. (a) Streptococcal septicæmia, 3 cases. Two treated by Orr method. (1) One case died. (2) One case recovered but only after two other long bones were involved. These latter treated by Orr method. One treated by minimal drainage and frequent packing. This case and (2) above are both well; no evidence of recurrence. (b) (Staphylococcal septicæmia) 7 cases. Five treated by Orr method all died. One treated by diaphysectomy died. One treated by minimal drainage, etc., recovered from the acute stage but died about 4 years later from recurrence.

It is of interest to note that those patients who recovered had a shorter stay in hospital and fewer complications if treated by the Orr method, and that the conservative form of treatment yielded the poorest results. This would seem to indicate that it is of the utmost importance to establish adequate drainage early and well, and, moreover, to keep the affected limb at rest and undisturbed. That the treatment of the disease is only by adequate surgical drainage is disproved by the cases in Group III. Here in the patients who recovered the tendency for development of the disease in other bones

did not disappear until after the blood culture became negative.

There are some who would criticize the use of surgical intervention in the cases of the last group on the grounds that the lesion in the bone is merely secondary to the septicæmia and that the child's condition is not benefited in any way, either by the trauma of the operation or by being subjected to an anæsthetic. In this hospital it is felt that surgical intervention should be carried out for the following reasons. First, simply because there is an overwhelming septicæmia it does not follow that the local lesion in the bone contributes nothing to the maintenance of such a state. Secondly, and possibly more important, is the fact that the old surgical dictum "Where pus is, let it out" still holds true. It is a well recognized fact that as a rule a collection of purulent and necrotic material acts to the detriment of the general state of the individual, and consequently his powers of resisting the disease are even further lowered.

TREATMENT OF THE GENERAL BACTERIAL INVASION

Because of the fact that this component is probably always present at some time during the disease a blood culture should be taken as soon as possible. If this is found to be negative then all efforts are directed to the local lesion in the bone. It is advisable to watch the red-cell count and hæmoglobin in order to prevent any development of secondary anæmia. Fluid intake should be kept up either by mouth or if necessary by intravenous administration.

In those cases which showed only a very slightly positive blood culture, three in number, it was found that in two of them, once the bone lesion was adequately drained and general supporting measures carried out, the blood stream rapidly became sterile. This is reflected in the drop in temperature and pulse as well as improvement in the general condition of the patient. In the third case which had a slight staphylococcal septicæmia staphylococcus antitoxin was given but it is difficult to say whether the drainage or the antitoxin was responsible for the disappearance of the septicæmia.

In the cases of Group III various methods have been tried to combat the septicæmia. In those having a septicæmia due to the hæmolytic streptococcus continuous administration of fluid by the intravenous drip method, plus fairly frequent transfusions, seems to have been of benefit.

There has been only one opportunity to use the newer chemical preparations (sulfanilamide) so that a proper evaluation of this form of treatment cannot be made. However, if properly used and its ill effects carefully watched for, it might well prove a valuable adjunct in the treating of certain types of hæmolytic streptococcal osteomyelitis associated with septicæmia.

In all cases of Group III that showed the *Staph. pyogenes* in the blood stream staphylococcal antitoxin was given. The results were most discouraging, for there was only one recovery, and no tendency to halt the formation of secondary abscesses in other parts of the body.

Method of administering staphylococcal antitoxin.—There are two ways of administering this serum.

1. Intramuscularly.—There is little or no constitutional reaction but certainly the rate of absorption is decreased tremendously (Chart 3).

2. Intravenously.—If given undiluted the danger of severe reaction is great and several deaths have been reported. It has been found that if the serum was diluted 10 c.c. to 10 c.c. normal saline, and then injected intravenously very slowly with the patient under anæsthesia, some decrease in the number of fatal results could be attained. However, this is not without its dangers (Chart 4).

In this hospital the serum has been given in conjunction with normal saline by means of the intravenous drip. A continuous drip is started and adjusted for the proper fluid intake for 24 hours as needed for any particular case. Then to this is added 5,000 units (12 c.c.) of the antitoxin. It has been possible to administer up to 20,000 units in 24 hours without the occurrence of any reactions. If there is any reaction the administration can be stopped or slowed according to the intensity of such a reaction (Chart 5).

SUMMARY

1. A group of cases of acute hæmatogenous osteomyelitis is presented.
2. An attempt is made to evaluate the treatment of the condition.
3. A method of administering staphylococcus antitoxin is given.

CONCLUSIONS

1. Surgical drainage is essential in the treatment of acute hæmatogenous osteomyelitis of the long bones.
2. This is best accomplished by the Orr method.
3. Surgical drainage is not contraindicated in cases of severe septicæmia accompanying acute hæmatogenous osteomyelitis.

4. The mortality rate is higher in those cases with positive blood culture showing *Staph. aureus* (87 per cent) as compared with those with streptococcal septicæmia (33 1/3 per cent).

5. In those cases with a staphylococcal septicæmia all recovered if the blood showed less than 8 to 10 colonies per c.c. Only one case out of eight recovered from a staphylococcal septicæmia showing in excess of 10 colonies per c.c.

6. Repeated transfusions and intravenous administration of fluid are of value, especially in the streptococcal variety of septicæmia.

7. Staphylococcal antitoxin does not appear of value in combating staphylococcal septicæmia associated with osteomyelitis as regards the formation of secondary abscesses and the final fatal outcome. In some of the cases it seems to

improve, at least temporarily, the general appearance of the patient and to reduce the number of colonies in the blood stream.

8. If the use of the serum is desired the method of administration by means of continuous drip is the one of choice.

9. A reduction in the mortality rate of acute hæmatogenous osteomyelitis with septicæmia cannot be accomplished until a more effective treatment for the septicæmia is available.

REFERENCES

1. ORR, H. W.: A new method of treatment for infections of bones, *Trans. Sect. Orthop. Surg., Am. M. Ass.*, 1923, p. 138; *idem*: Listerism, *Am. J. Surg.*, 1928, 4: 465; *idem*: The treatment of osteomyelitis and other infected wounds by drainage and rest, *Surg., Gyn. & Obst.*, 1927, 45: 446; *idem*: Osteomyelitis, *Cyclopedia of Medicine*, Davis, Phila., 1934, 2: 602.
2. HOBART AND MILLER: Osteomyelitis at the Cook County Hospital, *J. Am. M. Ass.*, 1936, 107: 1118.
3. WILENSKY, A. O.: Acute hæmatogenous osteomyelitis, *Arch. Surg.*, 1934, 34: 320.

THE CLINICAL VALUE OF AUTOPSIES*

By R. E. SHAW, M.D. AND W. J. DEADMAN, B.A., M.B.

Hamilton

ONE of the important points upon which the efficiency of the modern hospital is rated is its autopsy service, and particularly the percentage of cases autopsied. Consistent effort, diplomacy, and consideration of the feelings of relatives of the deceased in securing permission, will, over a period of years, create in most municipalities a healthy attitude toward this very important study of the end-results of disease, of the accuracy of the diagnosis, and of the efficiency of the therapeutic measures employed, and will largely overcome the natural reluctance of grief-stricken relatives to permit such examination. Appreciation on the part of the public of the value of autopsies, not only in the improvement of medical knowledge but in clearing up matters related to Workmen's Compensation and insurance, results, not infrequently, in voluntary requests for this service. The clinical diagnosis will naturally be verified in the great majority of cases, but in many of these secondary findings of value are not uncommon. In a minority of cases quite unusual or unexpected findings are encountered. The latter provide great interest, and the findings

are often of exceptional value, since they broaden in the mind of the clinician the range of possible diagnoses.

A series of about 300 autopsies performed at the Hamilton General Hospital during 1938 has been analyzed. This series included cases from all the services of a 550-bed general hospital. Over 50 per cent of the deaths were autopsied. With regard to age-groups, 10 per cent of the number were performed on infants up to the age of one year; 16 per cent were carried out on persons between the ages of 40 and 50 years; 16 per cent between 50 and 60 years; and 30 per cent from 60 years up. The pathological changes accounting for death were found in the respiratory system in 27 per cent, in the circulatory system in 20 per cent, in the alimentary and nervous systems 20 per cent each, and in the genito-urinary system 15 per cent.

Broadly classifying into groups the pathological lesions accounting for death, it has been found that, in this series, in almost 50 per cent of cases, death resulted from acute or chronic inflammatory processes. This is to be expected. It is from the study of this group of cases that the clinician derives most benefit. Therapeutic procedures find their most promising field in the management of diseases due to the derangement of the normal anatomy and physiology of

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organs and tissues resulting from the injurious effects of pathogenic bacteria, whether exerted suddenly or over a more extended period of time. In addition, the repair processes of the body have their best opportunity to bring about complete or partial recovery, or at least arrest, aided, of course, by the administration of therapeutic reagents and procedures of acknowledged value. A close study of the gross and microscopic appearances of the tissues in cases where all the reactive powers of the body and all the skill of the clinician have failed often points the way to improved treatment, or to the withholding of treatment which may appear to have no hope of success, or which may, in the occasional case, have been ill-advised.

Malignant neoplasms were found as the primary cause of death in about 10 per cent of the cases. It is interesting to observe that an analysis of tissue removed surgically reveals approximately the same percentage of malignant neoplasms. The post-mortem study of patients dead of malignant growths has a great value in the exact determination of the type, the site of the primary growth, the extent and location of metastases, and in the correlation of these findings with the clinical symptoms. The study of the degree of response of these growths to the therapeutic measures employed is definitely valuable. The occasional finding of unsuspected malignant tumours and of multiple primary growths is a matter of considerable interest and of clinical value.

The degenerative diseases, mainly associated with arteriosclerosis and its varied allied pathological conditions, such as coronary disease, cerebral hæmorrhage, and nephrosclerosis, account for about 25 per cent of the cases in this series. The clinical value of the study of these cases consists again mainly in the correlation of lesions with symptoms and in the constant development of the ability of the clinician in differential diagnosis. Unfortunately, little if anything can be done to repair the ravages of these diseases or to retard their progress, but the physician who can visualize the changes going on in organs and tissues is eminently better able to prognosticate the accidents likely to occur at some stage in the progress of the process and to advise measures which may tend to delay somewhat their occurrence.

The group of cases in which death is sudden and unexpected provides perhaps the greatest

interest. In the absence of post-mortem examination of these cases, there is a tendency to ascribe most of them to lesions of one of two organs, the heart or the brain. These deaths may on occasion be related to lesions of any of the systems or to those of many of the organs of the body, and it is admitted by all pathologists of experience that there is the very occasional case where elucidation of the cause of death baffles the best.

The following unusual cases encountered in the course of this series of autopsies will serve to illustrate these points.

CASE 1

A male, aged 29 years, had attended the Out-patient Department of the Hospital for two years previously, complaining of convulsions which had been increasing in severity for the past five years. Fifteen years before he had fallen down an elevator shaft, injuring his head and back. For the past five years seizures of a convulsive nature had been preceded by marked external rotation of the left eye. In 1938 he was admitted to hospital with extensive superficial ulceration of the skin surfaces from which he developed a streptococcus septicæmia and died. The autopsy showed, in addition to the picture of septicæmia, marked atrophy of the cortex and medulla, with shrinking of the right occipital pole, underlying which was a large cystic dilatation of the posterior horn of the right ventricle, instead of the usual findings associated with Jacksonian epilepsy.

CASE 2

A male, aged 60 years, who had been a stone-mason for the previous 40 years, was admitted to hospital in 1937 complaining of pain in the right chest, cyanosis, vomiting, weakness and loss of weight, over the past year. X-ray examination of the chest resulted in a diagnosis of silicosis. The next year he was admitted with similar symptoms, dying a few days later. The death was clinically attributed to silicosis. The autopsy revealed in addition to the presence of a moderate degree of silicosis, the gross appearance of a bilateral lobar pneumonia. Microscopic examination of the lungs, however, revealed the pathological picture of lobar pneumonia, and also a diffuse infiltration of the lung tissue by a type of adenocarcinoma primary in one of the bronchi. The association of carcinoma of the lung with silicosis is an unusual finding, although it recalls the reports of the development of cancer in cases of silicosis in the "Schneeberg miners' group".

CASE 3

A male, aged 45 years, was admitted to hospital in 1938 with complaint of sudden attacks of shortness of breath and cough. This shortness of breath had had a sudden onset 18 months before, during which time it had become progressively worse and more frequent. During his attacks in hospital, dyspnoea, rapid pulse and raised blood pressure up to 180/110 were noted. A hard mass, $\frac{3}{4}$ inch in diameter, was to be palpated at the attachment of the right sterno-cleido-mastoid muscle, which the patient attributed to an injury. No pulsation in the carotid artery or its branches above this mass could be detected. Pulsus alternans was present and considerable cardiac hypertrophy was present. Autopsy revealed the presence of a nodular thyroid with multiple adenomata, some of which were calcified. This had surrounded and compressed the trachea with consequent narrowing, and had exerted pressure on both carotid arteries and jugular veins, particularly the right, causing resultant raised

blood pressure and cardiac hypertrophy. The terminal cause of death was myocardial failure. This case illustrates an unusual clinical result due to prolonged mechanical pressure on neck vessels by a nodular thyroid, which, had it come to clinical notice at an earlier stage, might well have been removed.

CASE 4

A male, aged 67 years, admitted to hospital in 1938, with a clinical picture which justified the diagnosis of coronary thrombosis and cardiac infarction. Death occurred about three weeks after admission. Post-mortem examination verified the diagnosis. The heart showed a moderate hypertrophy, with coronary occlusion and infarction of the left ventricle wall. An additional finding was the presence in the liver of one cyst with some calcification, about 5 cm. in diameter, from the inspissated contents of which were demonstrated the typical hooklets of *Tænia echinococcus*. This cyst was of course in no way responsible for the death, but is an interesting collateral finding.

CASE 5

A female, aged 30 years, about two months before death suffered a moderate sunburn of the neck. A few days later, while riding in a bus, she jolted her arms, and thereafter noticed a generalized pain in her arms which did not respond to antirheumatic treatment. About one month after this, she developed a rash on her hands, with some oedema. An erysipeloid condition of the skin of her forehead developed, and the skin of the back and buttocks broke out into blebs. She ran a low temperature and the pains and aches became generalized throughout the whole body. She became gradually weaker and died. The physician in charge of the case made a clinical diagnosis of dermatomyositis. The autopsy confirmed this diagnosis, and revealed the condition of skin and the peculiar fish-flesh appearance and soft consistency of all muscles observed which are characteristic of the disease. The histology of the muscle tissue was typical. A terminal bronchopneumonia and toxic degeneration of viscera were responsible for the death.

A second group of cases provides great interest for the pathologist, and is of very considerable value to the clinician. This group includes those cases in which sudden or unexplained death occurs, with or without history of previous illness, and in which the lesion accounting for death is quite unexpected and of such a character as to make difficult or impossible ante-mortem diagnosis. Any series of autopsies of any magnitude is bound to provide such cases periodically, and the consideration of these cases, is, so far as the clinician is concerned, bound to improve his capacity for accurate diagnosis of causes of death, in those many cases which do not come to autopsy. This is bound to exert a corrective effect on the degree of accuracy of our vital statistics.

The following cases will illustrate.

CASE 1

A male, aged 54 years, was admitted to hospital suffering from severe shock. He had on the previous afternoon engaged in a competitive chess tournament and in the evening he was an intensely interested spectator of some of the games. During this process he became ill and collapsed on leaving the room. History on ad-

mission revealed the fact that he had suffered from hypertension for some time. The physical findings suggested a failing myocardium, and a diagnosis of coronary thrombosis with possible cardiac infarction was made, and was under the circumstances fully justified. At autopsy a moderately hypertrophied heart was found, but no coronary involvement. The pericardial sac contained 75 c.c. of blood and the left pleural cavity, 200 c.c. of blood. There was a marked hæmorrhagic oedema of both lungs and very slight subarachnoid hæmorrhage. The aorta showed an irregular rupture, 4 cm. in length, on the left side at a point 3 cm. from the aortic ring. There had evidently been a sudden rupture of the aorta at this point with dissection of the periaortic tissue and final bleeding into pericardial and pleural cavities. This accident is of rare occurrence, but will be encountered occasionally in any large series of autopsies.

CASE 2

A male, aged 66 years, was admitted to hospital unconscious, having developed paralysis of legs one week previous to admission. The diagnosis was cerebral hæmorrhage. He died two days after admission. At autopsy, cerebral hæmorrhage was indeed demonstrated, but in addition, and acting as the terminal cause of death, was found a rupture of the œsophagus just above the diaphragm. Through this perforation, a large amount of gastric contents had infiltrated the mediastinal tissues and had digested the pleura on both sides, so that a large amount of gastric contents was found in each pleural cavity. There was also an eroded perforation of the diaphragm through which had herniated part of the stomach and part of the left lobe of the liver. The reasonable explanation seems to be that an area of the œsophagus became infarcted and gave way.

CASE 3

A male, aged 50 years, suffered a fracture of the left mandible, which was wired, and which developed an intractable osteomyelitis, involving mainly the right ramus. Abscesses developed in front of the right ear and were drained. Subsequently, evidences of brain abscess developed which resulted in death. The autopsy revealed in the tissue in front of the ear, the presence of one small, flattened pellet of shot. In the cranial cavity was found an abscess of the temporal lobe, and on the floor of the middle fossa was found a small area of necrosing bone in which was another pellet surrounded by pus. Later inquiry elicited the information that he had received on that side of his face part of the discharge of a shot gun in an accident. The path of supuration was evidently along the inner portion of the mandible through an area of devitalized bone and up through the damaged floor of the middle fossa at the point where the lead pellet lay, a quite unexpected finding.

CASE 4

A male, aged 36 years, was admitted to hospital complaining of severe pain in the right upper quadrant for two weeks previously. In addition to his abdominal symptoms, there was tenderness and some enlargement of both breasts, particularly the right. A nodule the size of a small marble was felt in the right testicle. Laparotomy was performed, and tumour-like masses were found involving the periaortic glands, as well as an enlarged right kidney. The post-operative differential diagnosis was of Hodgkin's disease, tuberculosis of testicle and kidney, or malignant neoplasm of testicle and kidney. Autopsy revealed a primary tumour of the testicle, with metastatic growths in abdominal glands, liver and both lungs. Histologically, the tumour proved to be a chorion-epithelioma with the characteristic changes in the breasts. An Ascheim-Zondek test on a sample of blood taken from a blood culture flask, which had been secured the day before for blood culture gave a positive reaction. This is interesting as a case of undiagnosed chorion-epithelioma in a male, and from the fact that the

Ascheim-Zondek reaction was secured on a sample of blood which had been diluted with culture media and incubated for 24 hours.

CASE 5

A female, aged 69 years, was admitted to hospital with symptoms of abdominal distress and of intestinal obstruction. A vague history of gall-bladder disease was obtained. She died two days later. At autopsy intestinal obstruction was demonstrated but from a most unusual cause. The region of the ileocaecal junction was discoloured and a hard mass was felt at this point. Dissection of this region showed the presence at the ileocaecal valve of a large gall stone completely blocking the valve. Examination of the gall-bladder region showed pathological changes suggesting that the solitary stone had ulcerated through into the duodenum, and had passed down and blocked the valve, causing the obstruction from which she died.

In conclusion, one may say that the clinical value of autopsies resides not only in the confirmation or otherwise of the ante-mortem diagnosis, but to an even greater degree in the observation of the unusual and unexpected. In

the latter case, even more than in the former, the improvement in the differential diagnostic ability of clinician and pathologist alike will be progressive. The observation of the effect of such therapeutic measures as intravenous therapy on the lungs of fatal cases is an exceptionally good guide to the extent and manner in which such measures should be employed, and the value to the surgeon, in the observation of the efficiency and advisability of his operative procedure, will not be doubted. Vital statistics with regard to the cause of death are admittedly only approximately correct, and great improvement in their accuracy will come only from increasing post-mortem study.

BIBLIOGRAPHY

1. DEADMAN, W. J.: Unexpected autopsy findings in unexpected deaths, *Am. J. Clin. Path.*, 1931, 1: 127.
2. *Idem*: Findings of special clinical interest in post mortem examinations, *Canad. M. Ass. J.*, 1933, 28: 401.

Case Reports

TWO CASES OF DISLOCATION OF THE LENS

By P. B. MACFARLANE

Hamilton, Ont.

When a lens becomes dislocated into the vitreous by an injury, the question arises whether an attempt should be made to extract it or leave it alone. The following two cases are of interest in regard to the prognosis if the lens is left alone.

CASE 1

Mrs. W. reported for examination of the left eye in regard to glasses. She stated that the right eye was blind as a result of an injury twelve years before. On examination the right eye showed no surface inflammation, the iris was tremulous, the vitreous was clear, the optic disc atrophic. The dislocated lens, which was quite opaque, could easily be seen moving in the lower part of the vitreous. The tension was subnormal. The eye had never given her any pain and she had no complaint except that it was blind. The left eye was normal, requiring only her reading correction of three dioptries.

CASE 2

Captain B., aged 84, complained of the left eye being painful and very sensitive to light. On examination the conjunctiva was found to be very much inflamed, the cornea cloudy, the iris was atrophic and tremulous, and the pupil semi-dilated. The optic disc was white, with a deep glaucomatous cupping, and numerous patches of atrophic choroiditis were present. The edge of a dislocated lens could be seen in the lower part of the vitreous. The tension of the eye was very high. He gave the history that forty-four years before he had received a blow on the eye. After the immediate effect of the injury subsided the eye had never given him any pain

or discomfort but it gradually became blind. Several months before this examination the eye became painful and tender to touch. Of course the eye was enucleated. The right eye had normal vision and showed only the changes associated with a moderate amount of arteriosclerosis.

PREMATURE DELIVERY OF ANENCEPHALUS

By WM. J. STEVENS, M.D., C.M., F.R.C.S.(C.)

Ottawa

Fetal monstrosities are always a source of scientific curiosity and the subject is of particular interest when these conditions are demonstrated ante partum. The first report of such was made in 1916 by Case. This report covers such an abnormality which was suspected and verified by x-ray. From a clinical standpoint it presented the cardinal findings of sudden hydramnion, the absence of a palpable fetal head, but with an audible fetal heart.

As to the etiology of this abnormality nothing is known.

CASE REPORT

The patient was aged 32; she had one living normal child, aged 14 months. Her last period was July 15th, making her expected delivery April 21st. Her antenatal history was normal prior to February 24th (7 months) when her abnormally large abdomen suggested that she was either ahead of the expected time, or the presence of excess amniotic fluid. The fetal heart sounds were

normal. An x-ray by Dr. McNabb reported "There is a single fetus pregnancy with the occiput lying to the right and presenting. The fetal head appears small and deformed".

After I carefully explained the condition to the husband and later to the patient, an intelligent young woman, on March 3rd she was admitted to the Ottawa Civic Hospital. Immediate medical induction provided sufficient dilatation for bag insertion in 24 hours. She was given hyoscine analgesia and in 5 hours' time, on March 4th, the patient expelled by breech a female

anencephalic monster, weighing 2 lbs. 14 ozs. It was born alive and breathed for about 5 minutes.

The patient during her labour had perfect relief from pain. She was well pleased that she had been informed beforehand of the accident of Nature.

When an anencephalic monster is suspected antenatally and is verified by x-ray premature delivery lessens the disappointment, and saves the patient embarrassment.

Therapeutics and Pharmacology

HYOSCINE IN LABOUR

BY WM. J. STEVENS

Ottawa

Hyoscine as an analgesic and semi-hypnotic has been used for many years in obstetrics, either alone or in conjunction with various other drugs. When used alone in carefully regulated doses it gives excellent results, not requiring its mating up with any other drug. The coupling of hyoscine with morphine for instance (and this is true of many other drugs) certainly does tend to asphyxiate the baby and is definitely to be condemned.

Hyoscine is a strong cerebral sedative with amnesic properties. After the second dose, as herein prescribed, the patient is quieted, she becomes drowsy; later meaningless mutterings suggestive of delirium may prevail, her eyes may be open, but she more often fails to recognize her surroundings. Her face becomes flushed, her mouth dry, and her pupils dilated; respirations and pulse remain the same; blood pressure may be a little lower, she may pick at the air or bedclothes or become restless, even to the point of trying to get out of bed.

Technique.—Carefully written routine orders for the nurse and personal interest by the obstetrician assure greater success. The patient is prepared before commencing the analgesia. As with the use of rectal ether-oil or synergistic analgesia,* the patient is advised beforehand that she should co-operate as much as possible to obtain successful relief from pain. The environment should be quiet and kept so until the baby is born. Cotton may be placed in her ears. The nurse, who is required to be constantly with the patient, should not answer questions nor attempt to restrain the patient any more than is absolutely necessary. This is very important. The nurse keeps a careful routine tab on the fetal heart and perineal information. The bladder is watched; catheterization may be necessary.

The initial dose of gr. 1/100 of hyoscine is given hypodermically when the os in a primipara is dilated 2 fingers and the pains are

coming every 5 minutes, or, otherwise, when labour is apparently definitely established. As with any analgesic agent if given too late good results cannot be expected, as the hard bearing-down pains are too strong to be overcome. Succeeding doses of 1/100 gr. of hyoscine are given hypodermically every ½ hour until 4 doses are given altogether, and then the same dose is given every 1½ hours or every 2 hours depending upon the results obtained and the size and stability of the patient. It is important that the dose, if due, should be given just prior to the patient's being taken to the delivery room. A moderate amount of ether may be given by inhalation, if necessary, to quiet the patient or just at the birth. (When a patient has been given any analgesic very little anæsthetic by inhalation should be given, as more than is necessary tends to asphyxiate the fetus.)

At the birth baby is born unaffected by the drug and cries normally. Morphine, gr. ¼, may be given hypodermically an hour or later after delivery, to assure continuance of the patient's well being.

I have used hyoscine in this way in over 200 private cases and can recommend its use. It is safe. The treatment is carried out by the nurse and does not necessitate the obstetrician's presence. Results are very good from the standpoint of both mother and babe, and in practically all cases no memory of the labour or delivery is retained after the second injection. Labour is not perceptibly prolonged. Loss of blood is not excessive. If the pains weaken, the next injection is deferred until they are stronger. No intolerance to hyoscine was encountered and no contraindications. Some patients preferred synergistic analgesia. Complete amnesia was obtained in nearly all cases, otherwise the remembrance of pain was very hazy. All babies were born alive where the fetal heart was heard.

Perfection, of course, is hard to realize in any man-made device, but practically the only disadvantage in the use of hyoscine is the restlessness that it sometimes produces in the patient. This restlessness, while not always present, varies considerably, but in the case of a large strong woman attempting to get out of

* Stevens, W. J.: Rectal-ether analgesia in child-birth, *Canad. M. Ass. J.*, 1932, 26: 178.

bed, may demand considerable athletic prowess on the part of the nurse in restraining her. Sometimes accommodation of vision is disturbed for 24 hours but it passes off. However the fine results obtainable make this agent, when used alone and according to definite plan, very desirable.

In the home synergistic analgesia is more adapted, as the doctor is assured of a quiet patient permitting of more careful delivery. However, in the case of a placid patient, hyoscine may be used, provided of course constant watchful care is maintained on the mother.

THE SIGNIFICANCE OF THE DARK FIELD TEST IN THE EARLY DIAGNOSIS OF SYPHILIS

BY I. E. WEISSTUB, M.D., L.M.C.C.,

Port Arthur, Ont.

In this brief item I desire only to emphasize the value of the dark field test in the primary stage of syphilis. As is known, the primary stage is the most important one in connection with the elimination and radical extermination of the disease. I still remember the words of my teacher, Prof. D. Finger, of Vienna, one of the most outstanding authorities on venereal disease, who used to say that the success of the treatment of syphilis lies not in the hands of the specialist but in the hands of the general practitioner, who is responsible for diagnosing the primary lesion and curing the case. According to my observations many patients have been victims of inadequate, or no, treatment during this important primary stage, because

the general practitioner placed too much confidence in the blood serum diagnostic tests, which are unreliable at least for the first three weeks following the appearance of the primary lesion. In most cases at the beginning the infecting organism has not yet invaded the lymphatics and blood stream, and the attending physician makes a diagnosis of a non-specific skin affection, with the result that four or five weeks later he is surprised by the appearance of the secondary rash, thus lessening considerably the chances for quick and total recovery.

At this point I desire to emphasize that too much significance should not be attached to the copper colour of the primary lesion, so much emphasized by the older clinicians; further, that the single lesion is not pathognomonic. In cases where strong chemical antiseptics have been applied by the patient or his physician a second or repeat dark field test should be made after a few days' rest from local treatment. In some cases a secondary infection of the lesion, with free formation of pus, spoils the dark field test, probably because of phagocytosis, and therefore in such the blood serum tests are a valuable aid in diagnosis.

SUMMARY

1. The dark field test is more important in the diagnosis of syphilis in the primary stage than the blood serum tests.
2. The copper colour and singularity of the lesion are not pathognomonic, and their absence does not exclude syphilis.
3. It is important that physicians in isolated places should insist on their patients as early as possible visiting centres where both the dark field test and the blood serum tests are available.

Clinical and Laboratory Notes

ON THE PROTECTIVE ACTION OF TESTOSTERONE AGAINST THE KIDNEY-DAMAGING EFFECT OF SUBLIMATE*

BY HANS SELYE

Montreal

Experiments on the mouse indicate that resistance against sublimate poisoning is greatly increased by testosterone. The degenerative changes which usually develop in the kidneys under the influence of sublimate intoxication are not observed in mice receiving testosterone in addition to such doses of sublimate as produce

marked renal damage in otherwise untreated controls. This protective action of testosterone is evident in both sexes but is somewhat more marked in females than in males.

It is concluded that treatment with testosterone does not merely increase resistance to sublimate by enlarging the kidney and thus stimulating the compensatory hyperactivity of undamaged areas, but this androgen actually protects the tubular cells against the damaging action of sublimate. As an incidental observation, it is noted that the liver changes caused by sublimate are likewise prevented by testosterone.

Other androgens such as methyl testosterone, androstenediol-3-acetate-17-benzoate, dehydroisoandrosterone and androstenedione have a similar effect, and their ability to enlarge the kidney runs roughly parallel with their androgenic action. It is perhaps worth mentioning that in similarly conducted experiments with ethinyl testosterone, which is a rather inactive androgen,

* From the Department of Anatomy, McGill University, Montreal. Abstract of a paper read before the Montreal Physiological Society on December 18, 1939.

The expenses of this investigation were defrayed in part through a grant in aid received from the Schering Corporation of Bloomfield, N.J., who have also supplied all steroid hormones used in these experiments.

practically no kidney enlargement or protection against sublimate was obtained.

The possible clinical significance of this protective action of the hormone is considered, since if the human being reacts in a similar manner, treatment with androgens may prove efficient in patients suffering from tubular damage.

AN ACCOUNT OF A COMMUNITY SERVICE BY YOUNG PEOPLE IN SUPPLYING BLOOD DONORS, AND A DESCRIPTION OF SPECIAL TECHNIQUE OF GROUPING AND TESTING

By F. SMITH

Kelowna, B.C.

The voluntary donation of blood was suggested by one of our physicians, to the leaders of "Toe H" and the Junior Board of Trade as a laudable means of satisfying the urge of the members in fulfilling the gospel of their societies. Immediately volunteers were called for, young men and women came forward, soon bringing the available blood donors up to the number of 78, in a community of about 5,000. Before proceeding to group and blood-test these people it was considered advisable to ask them to sign an agreement showing their readiness to give blood if called upon. Not one objected to this; which placed the intention as real and not sensational or spectacular.

Arrangements were made for groups of 10 at a time to come to the laboratory. Blood was taken from the finger, by puncture between the nail and the first phalangeal joint. In order to get a sufficient quantity 0.2 c.c. Kahn pipettes were used.

A finger of the proposed donor's left hand was selected, and was rubbed vigorously for two minutes with alcohol-moistened cotton-wool. The patient held the pipette in the right hand. The finger was punctured to a depth of $3/32$ of an inch, and, while pressure was applied by the technician, the patient placed the tip of the pipette to the droplet of blood, at an angle of 60° . By this method 0.2 c.c. of blood was readily taken. One drop of blood was placed in 1.25 c.c. normal saline for the red-cell-emulsion, and the remainder placed in a Kahn tube to clot. From this is taken the serum for the macro-micro flocculation test for syphilis.

In the subsequent technique an apparatus was used by means of which the mixture of serum and cells on the slide is prevented from drying out and may be kept for long periods in case of

delayed flocculation; a glass slide, 6 inches long and $3/4$ inch wide, is ruled off in squares of $3/8$ inch side, made by etched double lines, to prevent fluids within the squares from overflowing from one to another.

On space (1) on this ruled slide is placed a droplet, from a capillary, or 4 mm., loop of group II serum; on space (2) group III serum; on space (3) group IV serum, for control. On space (4) one mixes, with a 2 and a 4 mm. loop, respectively, the patient's serum and special antigen for the test for lues. To each of the sera on the spaces (1), (2), and (3), is added a 4 mm. loopful of the donor's red-cell-emulsion. The slide is next placed within a special flattened test-tube, which, after being moistened at the rim to ensure a tight seal, is closed with a rubber test-tube cap similar to those used for stock cultures. The apparatus is agitated continuously for two or three minutes, to mix the serum and cells, and serum and antigen, and is left either in the incubator for 5 minutes, or at room temperature for 15 minutes, when the blood-grouping test is read; but the slide in the tube is left at room temperature over-night in case there should be delayed agglutination in the test for lues. In this closed test-tube the mixtures can be kept indefinitely without danger of drying and consequent false flocculation.¹

In considering the incidence of the different groups, for its ethnological interest we referred to the list prepared by Tiber,² which comprises the grouping of 40,000 people in different parts of the world, by such authorities as Hektoen, Moss, Karsner, Culpepper, Buchanan and Hagley, Ottenburg, Snider and Tiber.

Our comparison with the world average, is as follows:

Groups		Kelowna Laboratory	Universal average
Moss	Universal		
Gr. I	AB	6.15	4.42
Gr. II	A	44.61	40.25
Gr. III	B	9.23	10.1
Gr. IV	O	40.0	45.2

Before using donors matching is insisted upon, and the cells and serum of donor and recipient are tested for sub-group agglutinins and agglutinogens and for hæmolysins.

The use of dried blood and of banks of blood collected from placentas at birth has been considered, but use of the individual donor was considered still justifiable.

REFERENCES

1. SMITH, F.: The macro-micro flocculation test for syphilis, *Bull. Vancouver Med. Ass.*, 1933-34, 10: 11.
2. PEPPER, O. H. P. AND FARLEY, D. L.: *Practical Hæmatological Diagnosis*, Saunders, Phila., 1933, p. 202.

Editorials

SOME DIAGNOSTIC ASPECTS OF HEADACHE

IN recent years a number of experimental and clinical studies have been conducted which have done much to enlighten us as to the nature of certain types of intracranial headache. The work of Huber, Penfield,¹ and MacNaughton,² in particular, has shown that nerves and nerve-endings are present along the arteries of the pia and to a less extent along those of the dura, and Forbes and Wolff³ have demonstrated that the vessels of the pia contract and dilate with stimulation of the vagus and sympathetic nerves respectively. This, with the observations of Pickering and Hess⁴ on the headache produced by the intravenous injection of histamine, has led to the wide acceptance of the view that most intracranial headaches are vascular in essence. The exact details of the process at work, however, are not so clear. We are not sure, for example, how much emphasis we should lay on spasm of the arteries; on perivascular oedema, and on anoxia. The vascular theory as at present accepted does not seem to account fully for the relatively long duration of some headaches. It suggests that arterial spasm brings about ischaemia of the part followed by relaxation, this latter resulting in oedema, which causes an increase in intracranial pressure and excites a painful reaction. Another explanation, to which Professor Cohen leans,⁵ is that, on the analogy of cardiac pain, headache of this type may be explained on the basis of anoxia. We would not expect, however, that cerebral oedema could be repeated often or continued for long without organic changes occurring in the tissues affected, yet in the case of migraine we know that, after years, there is no evidence of organic change in the brain. A plausible explanation of the long duration

of certain headaches may be found in the work of Dale⁶ and Lewis on the production of histamine and its effects, plus the theory of allergy. In a sensitized area, owing to the combination of an antigen and cellular antibodies, with effusion through the capillary walls, the damaged endothelial cells may continue to give out histamine for a long time, with a continuous characteristic reaction. We know that allergic reactions can pass off without producing any structural damage, as, for example, in the case of urticaria. The headaches seen in connection with sclerosis of the cerebral arteries probably find a sufficient explanation in the local anaemia and concomitant anoxia which must result. Those associated with hyperpiesia are probably attributable to the tension of intracranial plethora. A similar explanation may, possibly, be admitted in the case of the so-called "psychogenic" or "functional" headache. The flushing of the face that is seen in the bashful person when confronted with some disturbing situation would be analogous.

It would appear, then, that intracranial headache is in most cases associated with changes in and about the cerebral vessels in certain rather restricted areas. While this tends to bring perhaps the majority of headaches into one main group, and is interesting to know, we may well doubt whether differential diagnosis has been much facilitated thereby. For the present, at least, we have to fall back on clinical observation, though at the same time we should not overlook the duty of attempting to join together any scattered links of evidence.

Headache is one of the commonest of symptoms, is often distressing, and in every case deserves full study. Even a mild headache may be significant of much. The temptation is to minimize its importance. It is well to remember that headache, after all, is only a symptom; its cause must be looked for.

1. PENFIELD, W.: *Arch. Neurol. & Psychiat.*, 1932, **27**: 30.

2. MACNAUGHTON, F. L.: *Proc. Ass. Res. Nerv. & Ment. Dis.*, 1937, **18**: 178.

3. FORBES, H. S. AND WOLFF, H. G.: *Am. J. Physiol.*, 1929, **89**: 266.

4. PICKERING, G. W. AND HESS: *Brit. M. J.*, 1932, **2**: 1097.

5. COHEN, H.: *Brit. M. J.*, 1939, **2**: 715.

6. DALE, H. H.: *Brit. M. J.*, 1934, **2**: 1161.

We should note, first, whether the headache is generalized or localized—frontal, vertical, occipital, or lateral; secondly, whether it is agonizing, severe, moderate or slight; thirdly, whether it is continuous, remittent, or periodic. It is usually easy to determine if the cause is situated extracranially, that is, in the integument of the skull (fibrositis, myositis, neuritis, neuralgia, herpes, toothache, abscess, traumatism). It is more difficult to determine whether, if the headache is intracranial, it is due to some local condition within the skull or to some remote systemic disturbance or disturbances.

It is, possibly, rather futile to attempt classification of headaches on a basis of etiology, for many have more than one cause operating at the same time, and any groups which may be demarcated are likely to overlap. Yet, a classification, however imperfect, has merit if it only calls attention to possibilities. The following is suggested as a starting point. It should be understood that by the term "intracranial headache" is meant pain felt within the head.

INTRACRANIAL HEADACHES*

Organic: Tumour; granuloma; cyst; arteriosclerosis of cerebral vessels; hæmorrhage; meningitis; encephalitis; disseminated sclerosis; contusion.

Vascular: General plethora; hyperpiesia.

Toxic: From specific fevers, nephritis, constipation, allergy, hormonal imbalance, anæmia, over-use of alcohol, tobacco, and other drugs.

Reflex (and/or toxic): This group is a large and motley one, embracing headaches due to lesions of many kinds and situated in many organs and regions of the body.

Functional (sometimes reflex): Migraine; asthenia, neurasthenia; psychasthenia; mental.

It is freely admitted that this classification has its defects, but at least it has the merit of calling attention to causes, to clues which

it is the duty of the physician to follow up. Certain headaches, such as those associated with migraine, uræmia, and intracranial tumour, are so striking clinically that these conditions come quickly into mind; others, less spectacular, such as those due to constipation or eye-strain, are also readily suggested. But many others that do not conform to so definite a clinical type may be overlooked, and are more difficult to orientate. These demand an exhaustive systemic examination and their elucidation may lead us into remote by-ways of medicine. It should be remembered that habitual headaches are practically always due to serious disease.

This subject is so vast that it is impossible to do it justice within the space available to us. But, in conclusion, we may refer to a few disjointed observations which have diagnostic value.

Eye-strain is a common cause of pain in the head, and nasal catarrh and sinusitis should also be mentioned. There is a curious and puzzling relationship between certain headaches and the eyes which invites further study. It has been found that pressure on the under surface of the tentorium cerebelli can cause pain behind the eye. Recurrent unilateral migraine followed by ocular paresis is almost diagnostic of basal intracranial aneurysm.⁷ Patients who go blind from intracranial tumours rarely suffer from headaches,⁸ and blind persons do not often suffer from migraine.⁹ No convincing explanation has been advanced for all this.

Migraine coming on after the age of forty is invariably due to gross intracranial disease.⁷ Recurrent "cyclical" vomiting with severe headaches in children usually means a posterior fossa tumour.⁷ But do not forget acidosis here.

A.G.N.

* Classification modified from Spriggs (*Brit. M. J.*, 1935, 2: 1).

7. COHEN, H.: *Brit. M. J.*, 1939, 2: 299.

8. CAIRNS, H.: *Brit. M. J.*, 1939, 2: 300.

9. CRITCHLEY, M.: *Brit. M. J.*, 1939, 2: 300.

PEPTIC ULCER

THE causation of peptic ulcer is one of the unsolved problems of medicine. Much clinical, pathological and experimental material has been gathered, and there is an abundance of theory on the question, but one aspect of the question has not yet received the attention it might. This concerns the frequency of incidence and the anatomical position of the ulcer. The matter has been dealt with in an interesting contribution by Dr. Gunnar Alsted,* of Copenhagen.

Dr. Alsted set out to examine certain general impressions which were obtained in his hospital: (1) that there was a steadily increasing number of admissions for peptic ulcers and similar dyspeptic conditions; (2) that this increase principally concerned male patients; (3) that gastric hæmorrhages were increasing.

His first discovery was in the nature of a by-product. On surveying the literature on peptic ulcer he was struck by the fact that duodenal ulcer is very rarely mentioned in the early accounts. Cruveilhier, whose studies between 1829 and 1842 make him the founder of modern gastro-pathology, never speaks of duodenal ulcer, and other writers of the time mention it only rarely. It was only towards the beginning of the 20th century that the diagnosis of duodenal ulcer began to be made more frequently, and nowadays, of course, it is well recognized as the most frequent of the two. Possibly this greater incidence is apparent only, and depends on improved diagnostic methods, but this is unlikely, since most of the early accounts were based on post-mortem material. Dr. Alsted next points out that there never has been any sure information as to the absolute frequency of peptic ulcer in the population. There are two ways of finding this out: (a) the pathologico-anatomical, which depends on post-mortem findings, and (b) the clinical, in which the number of clinical diagnoses are assembled. Both methods are defective, in that neither gives the absolute frequency at any one time, and also the information given is not complete in either case. However, post-mortem

methods are the more dependable. By assembling the figures of a large number of post-mortem reports, the conclusion seems warrantable that over the last 100 years or so at least 5 per cent of the population have suffered from peptic ulcer at some time of their lives. The clinical method is so uncertain and the figures based on clinical material are so variable as to be quite undependable as regards the incidence of ulcer. The conclusion is reached that the supposed increase in the frequency of ulcer is exclusively due to an improved diagnostic technique and a growing number of readmissions.

The sex incidence of ulcer is next dealt with, and here, also, according to the evidence from both the sources named, there has been a change in the last century. While in all earlier works the proportion of male to female was given as 1:5 or 1:6, it has gradually shifted, until recent figures show it as 3:1. This difference in sex incidence is also supported by the fact that hæmorrhage, perhaps the surest symptom of ulcer, is recorded as occurring in a parallel degree. That is, it used to be more common in females, but now that ratio is reversed. Again, perforated ulcer in earlier days occurred chiefly in women, but now the majority of perforations are in males. It is suggested that this change is linked up with the disappearance of chlorosis, and the effect of tight lacing is also considered.

As regards hæmorrhage, the evidence seems to support the view that it is more frequent now than in the last century. This is borne out by Dr. Alsted's own investigations in Copenhagen. It is remarked however, without any complete explanation, that during the years of the Great War there was a fall in the frequency of peptic ulcer, along with a decrease in hæmorrhages. It is held that peptic ulcers, which used to be predominantly acute, and to occur chiefly in the body of the stomach, have now become more chronic in type, and have shifted in general to the duodenum. This shift in position may account for the observation made in London in 1938 that the post-mortem material from two large hospitals over the period from 1897 to 1936 showed a

* Changing Incidence of Peptic Ulcer, G. Alsted. 148 pp. \$3.00. McAinsh, Toronto, 1939.

marked decrease in hour-glass stomach. The fact that ulcers have become more chronic in type is held to account for the greater number of admissions, some of which are re-admissions, and also for the growing frequency of bleeding, especially as melæna. Hæmorrhage also is less frequently fatal than formerly, but it must be borne in mind

that the treatment of acute hæmorrhage has altered of recent years.

Dr. Alsted has not explained the etiology of peptic ulcer. He concludes that no one etiological factor is involved. But his work is extremely valuable in its approach to the question, and his observations are full of interest and stimulus.

H.E.M.

Editorial Comments

The Interaction Between Various Steroid Hormones

The work of Dr. Hans Selye on the interactions of various steroid hormones presented in this issue of the *Journal* (p. 113), while admittedly of a preliminary and incomplete character, opens up for the first time on properly controlled lines a subject which promises to be of great practical value in the realm of therapeutics.

The more we study the functions of the various endocrine glands and the nature and relationships of their secretions, the more we realize how vast and intricate and astonishing the matter becomes. Indeed, we are in danger of being lost in a maze of new facts and speculations. Dr. Selye's discovery that when given in sufficiently large doses the steroid hormones have a pronounced effect not only on the sex

organs and the endocrine glands but also on the lymph nodes, the kidney, the liver and other organs and on somatic growth in general is far-reaching in its implications. He also finds that when certain combinations of hormones are exhibited one action of one hormone may inhibit a certain action of another hormone while the latter's other actions remain uninfluenced or are even enhanced. A study of the Table accompanying Dr. Selye's article will provide some surprises. One of the most notable of these is that when two certain steroid hormones, each of which when administered separately is competent to cause atrophy of the ovaries, when combined can cause the opposite condition—hypertrophy. The observation that the exhibition of corpus luteum hormone can bring about increase of body weight including growth in height opens up some interesting speculations.

A.G.N.

Medical Economics

IV.

THE DEFINITIONS AND FEATURES OF "HEALTH INSURANCE" AND "STATE MEDICINE"

By HUGH H. WOLFENDEN, F.I.A., F.A.S., F.S.S.

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The purpose of this article is to examine the various underlying conditions which must be satisfied by any plan before it can be classified as falling within the category of either "insurance" or "state medicine". The proper definition and understanding of these terms is of great importance, for both have been seriously misinterpreted on many occasions, with resulting confusion and sometimes even unnecessary controversy.

THE DEFINITION AND CHARACTERISTICS OF "INSURANCE"

"Insurance", in the form in which it has become known as one of the most beneficent

devices of the economic system, and whatever its administrative rules may be, involves a concept which is essentially simple in principle but complex in its details. That concept is, in brief, the co-operative association of a large number of persons, who agree to share amongst themselves the burdens resulting from the occurrence of a particular contingency—such as death, sickness, unemployment, etc.—by the payment of the necessary contributions into a common fund, from which benefits, related strictly to those contributions, are distributed in alleviation of the burdens against which the insurance is effected.

A plan of real "insurance" thus presupposes the co-operation of a large number of persons in a group, or groups; insurance apart from the group basis is impossible. The benefit which may be claimed by any individual on the occurrence of the contingency against which the insurance is effected may, of course, be more or less than the total contributions of that individual with interest and after deduction of expenses. Insurance is thus a device for sharing burdens—not for shifting them; if its operation

is financially successful the co-operative basis of the enterprise makes it possible for a contributor who has entered the plan on a "participating" basis to receive "dividends" equitably apportioned to his interest; if it is financially unsuccessful, any necessary reconstruction of the insurance fund ordinarily must require its members to share its losses as they would share its profits. There are, of course, some types of insurance organizations where this complete "mutuality" undergoes modification as a result of guarantees to the contributor, who then is generally in the position of a "non-participating" member—receiving his contract benefits and nothing more. It is not, however, necessary to discuss this matter here—the reader may find a further analysis in the author's "The Real Meaning of Social Insurance" (The Macmillan Company of Canada, Toronto, 1932), pp. 1-4, and 105-107, and "Unemployment Funds; a Survey and Proposal" (The Macmillan Company of Canada, 1934), pp. 167-173. The point of immediate importance is the concept of insurance as a co-operative group effort, in which all will share as their respective interests, equitably determined, may require.

This equitable determination evidently demands a clear understanding of the rules and regulations of the insurance plan. Obviously it is necessary that certain conditions must be fulfilled, both when each new contributor joins the plan, and during the whole of his connection with it. Without attempting to set out in too much detail the various forms in which these conditions may properly appear, it may be said that, in broad outline, the following requirements must be satisfied: (a) the contingency against which the insurance is effected must be specifically defined and understood, and it must be capable of verification and practical interpretation; (b) the contingency, to be covered by insurance, must involve either a loss in property or a loss in human value which can be evaluated in terms of money (although actual payment for the loss so evaluated may be made in kind, of course, and/or in money); (c) the probability of the occurrence of the contingency must be predictable within the limits of variation indicated by the laws of chance, and the contingency must be one which is not likely to occur simultaneously to every member of the insured group, and which will not be influenced unduly by the voluntary acts of those insured; (d) the group to be insured must be reasonably homogeneous, so that the rates of contribution may be computed equitably in accordance with the requirements of condition (c), and so that the subsequent appearance of inequitable relationships between the various members of the group may be forestalled; and (e) the rules and regulations governing the practical operation of the plan must be drawn and administered so that the contingency, the contributions, and the benefits are defined and understood, and so that the claims for benefits can be investigated, certified, and controlled in

order to make sure that they fall within the terms and conditions of the plan.

THE PRACTICABILITY OF HEALTH (OR SICKNESS) INSURANCE

When these requirements of a true "insurance" plan are applied to the contingency of sickness it will be seen that, under proper and careful administration, they can be met quite adequately. This conclusion, of course, has been substantiated by practical experience over a long period—certainly the last 140 years—during which the evolution of voluntary sickness insurance in Great Britain and Europe has developed a very large body of statistical and actuarial data of great value, which is now supplemented by important observations on this Continent. The actuary, who generally is charged, *inter alia*, with the duty of calculating and certifying the necessary rates of contribution to sickness insurance funds, and subsequently guiding their financial progress, is thus now in a position to embark upon the preparation of such computations for any scheme of health insurance with much invaluable material and the lessons of extensive experience. At the same time his approach must be restrained by a very salutary degree of caution—for the proof of alleged sickness, which must be made in order to establish the admissibility of any claim, is frequently not as incontrovertible as is the proof of death or the occurrence of a fire in life or fire insurance. The precautions imposed by this indefiniteness necessitate certain restrictive administrative procedures, designed firstly to eliminate malingering in the filing of claims, and secondly to make sure, by inspection and control of the medical certifications, that every claim does fall within the terms and conditions of the insurance plan.

CONDITIONS NECESSARY FOR AN ACTUARIALLY SOUND HEALTH INSURANCE PLAN

It will probably be sufficient in these articles to deal only briefly with the responsibilities of the actuary with respect to the financial guidance of sickness insurance funds, for I have had occasion to discuss them at length elsewhere in several papers accessible to the medical profession—particularly in "Insurance and Public Health" (Ontario Conference of the Ontario Health Officers' Association, the Canadian Public Health Association, and the Ontario Medical Association, 1934—*Canadian Public Health Journal*, July, 1934, p. 307, and *Manitoba Medical Association Review*, September, 1934, p. 13); "The Problem of Health Insurance" (Eleventh Annual Convention of the Ontario Hospital Association, October, 1934, and *Manitoba Medical Association Review*, December, 1934); and "The Financial Implications of Compulsory Health Insurance" (Sixth Canadian Conference on Social Work, Vancouver, 1938—*Bulletin of the Vancouver Medical Association*, July, 1938, and *Manitoba Medical Association Review*, February, 1939). The following summary of the actuarial

matters discussed in those papers, however, may be given here:

(a) The "actuary"—a term first used in the deed of settlement of the old Equitable Society (founded in London for the insurance of lives over 175 years ago), and derived from the Roman "actuarius" who recorded the "acta" of the Roman Senate—many years ago undertook the compilations of the registers and then naturally the computations required in respect of life and sickness insurance, and gradually has become charged with the duties of performing all the statistical, mathematical, and financial calculations which form the basis of any plans involving the contingencies of human life (birth, death, sickness, accident, disability, unemployment, etc.).

(b) One very essential aspect of these computations lies in the assessment of the somewhat intangible influences which ultimately determine the collective experience of the whole of a measurable group—even though the prospects of any individual of course cannot be predicted.

(c) The technique of actuarial procedure therefore must emphasize the importance of maintaining safeguards and controls which will not permit an individual to exercise "selection" to his own advantage, and against the equitable interests of the group of which he is a member.

(d) These considerations lead to the prescription of the following as necessary conditions before a plan can be certified as "actuarially sound": (i) The benefits offered must be defined, and the conditions for their payment must be clear; (ii) the corresponding contributions, or other financial arrangements, by which the costs of such prescribed benefits are to be met, must be determined by proper actuarial calculation; (iii) any power to alter the basis, terms, or conditions of the scheme must be subject to an actuarial certification that the costs of such alteration are within the financial capacity of the plan; and (iv) adequate machinery must exist for the certification, inspection, and control of claims for benefits, in order to make certain that they fall within the terms of the scheme, and for the impartial and judicial interpretation of the numerous and difficult administrative problems which inevitably arise.

(e) In the actuarial computations it is necessary to take account of the dependence of the rate of sickness upon age, sex, marital condition, occupation, personal and family history, locality of domicile, and economic status, and also to give effect to the influences of the provisions of the plan which define the following significant factors: (i) The "qualifying period", *i.e.*, the period which must be passed before the insured person first becomes eligible to file a claim; (ii) the "waiting period", that is to say, the number of days of sickness which must elapse before payment of any cash benefit shall commence; (iii) the "benefit period", being the length of time for which benefits will be paid; (iv) the so-called

"periods of attack", generally used in the case of benefits-in-cash, by which the claims are segregated according to their incidence in, for example, the "first three months" of claim, the "second three months", the "second six months", etc.; (v) the "re-qualifying period", during which eligibility must be re-established after exhaustion of any benefit period; (vi) the relation of the character and amount of the benefit to the normal standard of living and earnings of the claimant prior to the occurrence of the sickness; and (vii) the nature and size of the organization through which the payment of benefits is obtainable, and the facilities for and regulations governing the filing of claims, their medical certification, and their final scrutiny.

"SOCIAL INSURANCE", AND THE DISTINGUISHING FEATURES OF GOVERNMENTAL HEALTH INSURANCE

The preceding discussion has contemplated mainly the conditions necessary for the successful operation of voluntary health insurance plans. In recent years a general designation, namely, "Social Insurance", has been adopted widely to denote methods of securing money income, or other benefits in cash or in kind, on the principles of insurance, to workers and their families in the cases of sickness and invalidism, old age, death, and unemployment, when the State, in whole or in part, undertakes the creation and administration of such schemes, frequently prescribes the bases upon which employers or employees, or both, are obliged to contribute, and often assumes the ultimate responsibility for the financial sufficiency of the plans. It is to be noted, however, that all insurance is "social" in the truest sense; the phrase "Social Insurance", accordingly, really should not be reserved, as it usually is today, for describing only governmental schemes. The entry of the government simply changes the channels by which the collection of the contributions and the payment of the benefits are effected; it is therefore important to realize that, apart from the introduction of the compulsory principle in conjunction with a theoretically unlimited taxing power, governmental operation merely substitutes one set of problems for another, with a change in their direction but not in their extent.

In these governmental schemes of insurance the attitude and relation of the beneficiary is of paramount importance. It is too often assumed that enterprises which cannot be conducted successfully by an association of individuals, such as an insurance society, can always be undertaken by that other co-operative type of organization known as government. And in the world of today we have learned all too thoroughly that the entry of government into any field of activity which may previously have been administered with intelligence, ambition, sympathetic understanding, and good results by individuals or co-operative groups of individuals, may intro-

duce, often with pronounced and surprising rapidity, a tendency for those same individuals to exploit the government without regard to any of the ethical principles which previously guided their activities. With the experiences of the last ten years before us it is not necessary to do more than draw attention once again to the significance of these influences. If, however, the reader should wish to pursue this line of thought more fully, discussions may be found in the previously-mentioned "Unemployment Funds", pp. 150-159, and in the author's papers on "The Meaning of Social Insurance" (The Third Canadian Conference on Social Work, Winnipeg, 1932), and "The Philosophy and Principles of Social Insurance" (an address before the Canadian Club, Ottawa, 1932—printed by the Canadian Life Insurance Officers' Association, Toronto). These analyses emphasize the importance of the "minimum requirements" of good citizenship; we cannot demand the maximum by way of protection, and yet be unwilling to give something adequate in the nature of a minimum return. Refusal to face the significance of this fundamental precept has already led to a great deal of confused thinking with respect to the relation between the State and the citizen as a potential beneficiary under governmental health insurance schemes.

THE NATURE OF "STATE MEDICINE"

Many debates in recent years have been precipitated through misunderstanding of the sharp distinction which in reality differentiates "state medicine" from health "insurance". The belief has been prevalent in many quarters that the economic device of "insurance" can be interpreted and operated in practice, in respect of the contingency of sickness, simply as a method which will "make secure", in the sense of providing cash payments and/or benefits in kind as of right to any person who may fall ill, without restriction, for an indefinite period, and regardless of contributions, conditions, or control. It is hardly necessary in these articles to elaborate upon the fatal weaknesses of such a view; a more extended discussion on the same matter with respect to the analogous problems of unemployment insurance may be found on pp. 6-7 of my "Actuarial Report on the Rates of Contribution for the Unemployment Insurance Benefits and the Provisions with respect to Supplementary Unemployment Benefits" under the Canadian

Employment and Social Insurance Act of 1935 (The King's Printer, Ottawa, No. 158-1935). For the purpose of explaining the difference between health "insurance" and "state medicine" we may simply recall that the essence of "insurance" is the payment of contributions by or on behalf of the members of a reasonably homogeneous group into a common fund, and the distribution of benefits to those members—and to no others—on certain definite conditions.

"State medicine", on the other hand, involves a wholly different approach. It presupposes, as a primary requirement, that the doctor (and others who would be called upon to render services) would be employed by, and would be under the direction and control of, the State, which under such circumstances would evidently be in a position to dictate procedures, modes of payment, and to prescribe and enforce penalties. The nearest approach to an official description is that stated in the House of Commons at Ottawa on March 7th, 1938, when Dr. T. C. Routley was quoted as follows: "The Canadian Medical Association has not adopted any official definition of the term 'state medicine', but it is my view that the Council would likely be in agreement upon the following definition: 'By state medicine is meant a system of medical administration by which the state provides medical services for the entire population, or a large part thereof, and under which all practitioners are employed, directed, and paid by the state on a salary basis' ". With the addition of the words "or otherwise", in order to embrace the possibility of some mode of payment other than by way of salary, this explanation would seem to be quite adequate.

The essence of the method is, of course, State compulsion and control. The re-orientation which it would effect in all existing medical relationships and practices needs no comment in this *Journal*. An example of extreme governmental provisions for regulations and penalties is pointed out in my address on "The Financial Implications of Compulsory Health Insurance", to which reference has already been made. The ultimate powers which almost certainly would be assumed by any Commission or other governmental body charged with the administration of such a plan do, therefore, merit most careful examination by the medical profession, and indeed by all who might either provide or receive services thereunder.

Planning for the future instead of living in retrospect is the most effective method of adjusting oneself to life after the age of fifty. Think only of tomorrow, plan for tomorrow, and prevent your brains from calling up thoughts of yourself in the past tense. No matter how young and vigorous you may feel, take time out for rest. The languorous fatigue that makes an arm-chair feel friendly to your bones and muscles is not at all harmful, even does good. It is that dead-beat weariness that weakens you and lessens your resistance to colds and influenza. Keep in mind that digestion uses up a lot of energy, especially when

the stomach is overloaded. Weight is the big bugbear of the majority of men and women as they pass the half-century milestone. Moderation should rule in all you do to take off weight. Reducing more than 2 pounds a week is likely to be harmful. The rate of weight loss is less important than that progress be steadily made. When you find you aren't getting winded so often from slight exertion, you may know you are on the right road. Walking is still man's best standby in keeping a good circulation, firm muscles, and a dependable breathing apparatus.—Carl Bond, in *Hygeia*, Jan., 1940.

Retrospect

ACUTE ENDOCARDITIS*

BY A. H. GORDON

Montreal

As one looks for a background to Osler's very substantial contribution to the knowledge of acute endocarditis, it is perhaps worth while to look into the current medical teaching in England and America ten and fifteen years previous to the date of the Goulstonian Lectures delivered by Osler before the Royal College of Physicians in London during March, 1885. As examples, we may quote from Austin Flint's "Practice of Medicine" published in 1868.

"Endocarditis and pericarditis are not infrequently associated in cases of rheumatism. Endocarditis, either with or without pericarditis, is developed in a certain proportion of cases in the course of Bright's disease. It is stated also to occur occasionally in the eruptive and continued fevers and in cases of pyæmia. It may possibly be produced by contusions of the chest. It may be associated with pleuritis or pneumonitis when it occurs in rheumatism or in other pathological conditions."

Bristowe's "Theory and Practice of Medicine", published in London in 1876, states:

"The causes of inflammation of the lining membrane of the heart's cavities are to a large extent identical with those which excite pericarditis and myocarditis. It is occasionally the result of the accidental rupture of valves or chordæ tendineæ. More commonly it is due to exposure to cold, but by far its most frequent cause is the presence of rheumatism. It may also be caused by extension from abscesses in the muscular parietes. Again, like pericarditis, it is often developed in connection with chorea and scarlet fever. A chronic form of endocarditis may occur in connection with the syphilitic cachexia, chronic alcoholism, Bright's disease, and other affections inducing a chronic dyscrasia."

These summaries, to say the least, suggest a limited conception of endocarditis.

But the days before Osler were not without their prophets. William Senhouse Kirkes, of St. Bartholomew's Hospital, in the *Medico-Chirurgical Transactions* of 1852, wrote a paper "On some of the principal effects resulting from the detachment of fibrinous deposits from the interior of the heart and their mixture with the circulating blood". It might well be read by every student as a model of case reporting. He accurately describes a group of cases of sub-acute endocarditis with cerebral embolism, but without attaching the name. I quote his conclusions.

"After careful perusal of all that I can find bearing on this subject in Rokitsansky's great work on pathological anatomy, I cannot find that he in any place even

hints at the explanation I have ventured to offer of the real cause of the secondary deposits in distant organs in cases of valvular disease of the heart. His observations seem to show quite plainly that he ascribes them to a poisoned state of the blood, consequent on the admixture of the products of the endocarditis with this fluid, whereby it acquires an increased tendency to coagulate. . . . The view, however, which I have ventured to take is that the deposits in the various organs are the direct mechanical results of the arrest of solid particles of fibrin detached from some part of the heart or arteries and too large to traverse the minute capillary canals to which they are brought by the circulating blood. By the obstruction which their arrest occasions they may induce coagulation of blood behind them; while by their mere presence they may act as local irritants, and so induce secondary processes of inflammation and suppuration like any other foreign body."

In 1870, Samuel Wilks, in the *Guy's Hospital Reports*, wrote an article entitled "Capillary embolism or arterial pyæmia" which is of great interest as it gives an accurate description of what Osler, fifteen years later, called malignant endocarditis, and while Wilks recognized the symptom-complex he did not quite reach the vision of the disease as a whole which Osler was later to see.

Wilks' paragraph reads thus:

"In these cases of arterial pyæmia it is probable that the first symptoms which attract attention will be the constitutional ones, and that febrile symptoms and occasional rigors will suggest the existence of ague. In fact I have seen cases of pyæmia, both venous and arterial, treated for miasmatic fever. After a short time it is possible that the liver and spleen may be felt enlarged, and still the obscurity remain. At a later period a bruit may be heard which may be styled aortic or mitral, according to its position. The febrile symptoms continue, and the patient, after a protracted illness, dies, and the organs are found affected as described, and vegetations are found on the valves of the heart. There may be appearances suggesting an old cardiac disease and accounting for the deposition of fibrin, but it is equally probable that there may be nothing on the heart to indicate an older change than that observable in the solid viscera. I have now seen so many instances of this both in hospital and private practice that I recognize them as belonging to a class, although I am often unable to state the origin of the blood change."

In 1885 Osler, then thirty-eight years old and professor of Clinical Medicine at the University of Pennsylvania and recently arrived from Montreal, delivered the Goulstonian Lectures before the Royal College of Physicians of London and took as his subject "Malignant endocarditis", a name coined by him to fit the clinical features of the disease. In his introductory remarks he stated that, in view of the clinical, anatomical, and etiological information which had been thus far ascertained, he proposed to summarize that knowledge on the basis of 200 cases collected from the literature and from the considerable experience which he had had with the disease at the Montreal General

* Read at the Seventieth Annual Meeting of the Canadian Medical Association, the Osler Hour, June 23, 1939.

Hospital, and it is interesting to us here to note the names of Molson, Ross, and Wilkins mentioned as in charge of these patients.

In these three lectures Osler points out that the disease may occur: (1) as a primary disease of the lining of the heart or its valves, either attacking those in good health or more often the debilitated and dissipated, and those with old valve lesions; (2) as a secondary affection in connection with many diseases, particularly rheumatic fever, pneumonia, scarlet fever, diphtheria, ague, etc.; (3) as an associated condition in septic processes, traumatic or puerperal diseases. He indicates also that the lesions are by no means uniform, and may be vegetative, ulcerative, or suppurative, and that these forms may occur alone or in combination. He found micrococci to be constantly present in the vegetations, but, from our standpoint, his description of them was very vague. He found the mitral valve involved alone in 77 cases, the aortic alone in 53, the aortic and mitral together in 41, the tricuspid in 19, the pulmonary in 15, and the heart wall in 33. The right heart alone was involved in only 9 instances. In severe forms hæmorrhages into the skin and mucous membranes were frequent. Emboli of the spleen and kidneys and brain were frequent. He described the types of onset as febrile, cardiac, and embolic, and among the febrile group there were some cases which simulated malaria in their regularly intermittent type of fever. Some cases were admitted with cerebral and meningeal signs, and these were associated with pneumonia.

For us, fifty odd years later, who still find the diagnosis of this disease a matter of no small difficulty, it is easy to understand Osler's statement that "in the hands of skilled physicians" in 1885 "the diagnosis of at least 50 per cent of the cases was made post mortem", and it is a tribute to the great master that he pointed out the road and put up plain signs to make recognition easier to those who came after.

Of the 209 case histories of acute endocarditis which Osler examined there were 37 following pyæmia. In 45 cases there was no record of antecedent disease, in 127 cases there was a history of some disease with which the cardiac trouble might have been associated, and in 53 of these that disease was rheumatism, but in only 24 did the graver form of endocarditis occur during the progress of the acute rheumatic attack. Of all the 209 cases of malignant endocarditis there were only three or four under 11 years, and the same number over 50 years, the great number appearing in middle life.

In 103 patients dying of pneumonia in the Montreal General Hospital 11 instances of malignant endocarditis were found. Fränkel had described the pneumococcus only a year before Osler delivered the Goulstonian Lectures and the relation of this organism to pneumonia was yet debatable. Bacteriology as we know it was just awakening, and in this light, Osler ap-

pears to have assumed the mantle of the prophet when he gave his view of the nature of the disease he had been discussing in these words:

"Briefly stated, the theory of acute endocarditis which at present prevails, and the only one to which I shall refer, is that it is in all its forms an essentially mycotic process, the local and constitutional effect being produced by the growth on the valves, and the transference to distant parts of microbes which vary in character with the disease in which it develops. This very attractive theory can be adjusted to meet every requirement of the case, though as yet lacking certain of those substantial data necessary for full acceptance, but which, having been furnished of late years in other diseases, we may hope will in time also be forthcoming for this."

In 1908 Osler read before the Association of Physicians of Great Britain and Ireland, a paper entitled "Chronic infectious endocarditis" in which he reported 10 cases of a type which, he stated, he had not seen at the time of the delivery of the Goulstonian Lectures. These cases were characterized by prolonged fever running from four to thirteen months. The fever was of a remittent type, not showing the malaria-like paroxysms which he had before described, and rarely rising above 102 or 103°. Eight of these cases showed evidence of mitral disease and two of aortic disease, and the murmurs changed but little in spite of the presence of extensive recent vegetations. There were relatively few symptoms of cardiac disease, such as palpitation or breathlessness. It was in this group that Osler laid emphasis upon the embolic manifestations in the fingers, described by Dr. J. Heurner Mullin, of Hamilton, in these words: "The spots come out at intervals as small swollen areas, some the size of a pea, others a centimetre and a half in diameter, raised, red, with a whitish point in the centre. I have known them to pass away in a few hours, but more commonly they last for a day and even longer. The commonest situation is near the tip of the finger which may be slightly swollen." Osler points out, also, the presence of other embolic features, as in the retina, the spleen, the kidney, and the vessels of the brain or limbs. It is in this article that he mentions the value of blood cultures in making a diagnosis. In the same year T. J. (now Sir Thomas) Horder reported 115 cases of infective endocarditis from St. Bartholomew's Hospital in the previous 7 years, which were 0.6 per cent of the medical admissions, and in 40 cases positive blood cultures were made.

A long leap forward in the knowledge of this disease was made in 1910 when Libman and Celler made blood cultures in 36 cases having the clinical features described by Osler, to which Libman adds: "the waxy, dirty waxy, or whitish colour of the skin", later described as the *café au lait* tint. In 35 of the cases an atypical streptococcus was recovered, later named the *S. viridans*, and, while it was relatively harmless when injected into animals, in every human case followed, in which the blood culture was positive,

the patient died. Libman's work established that the recovery of this organism from the patient's blood was the final proof of the presence of subacute bacterial endocarditis. I well remember the enthusiasm of our lamented colleague, H. A. Lafleur, on his return from the meeting of the Association of American Physicians where this work was presented.

We are indebted to Libman also for the terminology now generally employed—"Bacterial Endocarditis" for all cases proved to be due to bacteria (Rheumatism has not yet been so proved); "Acute", "Subacute" and "Chronic", according to their clinical course; and when the organism is determined, its name replaces the word bacterial—thus "Acute Pneumococcus Endocarditis". Libman in 1912 brought forward the view that the disease might pass into a bacteria-free stage, and Baehr has described an embolic glomerular lesion occurring in the an-hæmolytic streptococcus endocarditis.

One advance in our knowledge beyond that in Osler's time is our ability to break up the group of "malignant endocarditis" into "acute" and "subacute", a division which he foreshadowed in his recognition of the severity of those cases associated with pneumonia, and which modern bacteriology has been able to confirm.

We now identify the clinically "acute" forms of endocarditis with the pneumococcus, the Staph. aureus, the S. hæmolyticus and the gonococcus, and the subacute forms with the an-hæmolytic streptococcus and occasionally the bacillus of influenza.

It is regrettable that the therapy of the disease has advanced but little beyond the position in 1885. Many efforts have been made by the use of vaccines, transfusion from vaccinated donors, and intravenous injection of antiseptics with no apparent benefit. Transfusions have been of service in combating the anæmia. So far, our therapeutic efforts are limited to the care of the patient. The cure of the disease lies with the future.

What is the relation between subacute endocarditis and rheumatic endocarditis? The very frequent appearance of the one upon the site of the other must be more than a coincidence. Why does a relatively innocuous organism like the streptococcus non-hæmolyticus cause such havoc upon the heart valves? May its presence be but a coincidence also? These questions were asked by George Blumer in his review of the subject in 1923 and they are still unanswered.

While the outlook for the individual patient with this disease is scarcely any brighter now than it was in 1885, the work which Osler did upon the disease itself would mark him as a master, had he done nothing else. It exhibits the genius and the insight which took widely scattered bits of knowledge and pieced them together with the sweat of honest mental toil, to

make a strong and enduring platform on which others may stand to reach for still newer knowledge and complete a structure so well begun.

AORTIC SYPHILIS*

By J. HEPBURN

Toronto

One of Osler's many precepts to the young physician was that he should confine his reports on medical matters to work from the laboratory, leaving clinical comments, written and otherwise, to older, more experienced physicians. Osler lived up to this dictum fairly well, as far as aortic syphilis was concerned, at least in his early days at the Montreal General Hospital. His first publication on aortic syphilis was in 1876, and it consisted in reporting an autopsy on a case of aneurysm of the aorta, without any comment.

In 1877 the first of the Montreal General Hospital pathology reports appeared, in the preface to which Osler quoted Wilks, who stated that "Pathology is the basis of all true instruction in practical medicine". It is highly probable that many present day clinicians would put up a strong argument for substituting the word "physiology" for "pathology" in that quotation. That pathology report from the Montreal General Hospital was the first from a Canadian hospital, and was dedicated to James Bovell, Emeritus Professor of Pathology, Trinity Medical School, Toronto.

Three cases of aortic aneurysm appeared in this volume—one, a man of 32, died of pulmonary tuberculosis, and at post-mortem examination was found a large aneurysm which had eroded three dorsal vertebræ without symptoms.

The next volume of the Montreal General Hospital pathology reports followed in 1879, and included reports of 5 cases of aortic aneurysm. The main points of interest in these cases were that one was 35 and two others 40 years of age. In one of the older cases the aneurysm perforated the duodenum, a very rare complication. Perhaps the chief interest lies in the fact that the clinical notes were made by Dr. George Ross.

In 1880 Osler reported an autopsy on a case of aortic aneurysm, and quoted Dr. Ross as follows,—“Cases of thoracic aneurysm are sufficiently common here that I should not have deemed it worth while presenting this instance were it not that there are a few points of practical interest and value, both with reference to diagnosis and treatment”. Dr. Ross then commented on the recent observation by an army surgeon,—of tracheal pulsation as a diagnostic point, and he stressed the need for dry diet,

* Read at the Seventieth Annual Meeting of the Canadian Medical Association, Osler Hour, Montreal, June 23, 1939.

potassium iodide, and rest. In the years immediately following 1880, Osler published pathological reports of several cases of aortic aneurysm without any comment.

As President of the Canadian Medical Association, which met at Chatham in 1885, Osler, discussing a case of aortic aneurysm presented by Dr. Grant, of Ottawa, stated the prognosis was not determined by the size of the aneurysm, as he had known patients with large aneurysms to live 10 years, while small aneurysms might burst quickly. It depended on their location, *e.g.*, aneurysms of the descending aorta might exist a long time. He added that potassium iodide relieved pain, but he did not think it helped in consolidating the tumour. Here we see him entering the clinical field for the first time, as far as aortic syphilis is concerned. For a few years after this he confined his reports on this subject to post-mortem descriptions, without clinical comment.

In 1888 he gave one of his clinical talks which later became so characteristic. This time he illustrated the value of careful examination of peripheral arteries in disease of the heart and aorta, by referring to a man of 42, with dyspnoea and feelings of distress about his heart, visible carotid and radial pulsations, normal findings on percussing the vessels at the base of the heart, aortic systolic and diastolic murmurs. Dr. Wise told Osler that he could feel no arterial pulse in either lower extremity. Osler then rechecked the aorta and again found nothing abnormal, till he examined the back and found a pulsating bulge in the left interscapular space. He diagnosed an aneurysm with a large enough sac to absorb the entire pulse wave—hence no pulse in the legs. Many of us would find difficulty in accepting this as the only cause of absent pulse in the legs.

He published notes on aneurysm in the *Journal of the American Medical Association* of 1902, and, among other matters, referred to a case which came to autopsy and showed that a small aneurysm of the ascending aorta had ruptured into the superior vena cava. During life there had been a continuous basal murmur with a systolic exacerbation. He stated that such a murmur meant either abnormal communication between heart chambers or great vessels or between an aortic aneurysm and the superior vena cava or pulmonary artery. He quoted two further cases, both in men of 30, with such a murmur. In one case the aneurysm opened into the right pulmonary artery and in the other, into the superior vena cava. In this article he mentioned, for the first time the value of fluoroscopy in the diagnosis of obscure cases of aneurysm, particularly in those cases showing symptoms but no signs. The paper ended with a homily on the value of careful inspection of the chest—a bare chest—a good light—good eyes—a routine—especially inspection of the back, and he quoted several cases in which inspection of the

left interscapular region yielded the diagnosis. A year later he stated that "aneurysm of the ascending arch may cause no signs or symptoms till rupture occurs; aneurysm of the transverse arch, as a rule, produces both signs and symptoms; aneurysm of the terminal part of the arch, and of the thoracic aorta, produces symptoms but often no physical signs".

In 1903, writing on 14 cases of aneurysm of the descending aorta, he stated that 13 were male, symptoms were often latent, marked loss of weight was common, and that while the prognosis of aortic aneurysm in any site was bad he knew of cases in the descending aorta of 25 and 30 years' standing. His treatment at this time (1903) was free bleeding, complete rest, Tuffnell's low fluid and low calorie diet, and potassium iodide.

Illustrating the disappearance of aneurysmal symptoms, he reported in 1904 the case of a young man who had developed lues 8 years previously, and who for 2 years had suffered from pain in the neck and right shoulder, husky voice, etc., and three months prior to his examination by Osler a swelling had appeared above the sternum. With the appearance of the swelling, the pain, huskiness, etc., disappeared. Osler attributed the disappearance of symptoms to the fact that the sac had been able to expand into the soft tissues of the neck.

The Lancet of 1905 has a paper by Osler on aneurysm of the abdominal aorta. He made a statement which I am sure you will all agree with from your own experience, namely, that abdominal aneurysms are often diagnosed when not present, and, conversely, when present, often present obscure symptoms, and are therefore overlooked. Only 2 of his 16 cases were women, and he emphasized this because a throbbing aorta is much commoner in women. He pointed out, not for the first time, that cartilage such as the intervertebral disc resists destruction, but I think wrongly attributes this to "yielding—they do not feel the pressure". Our present belief is that they resist destruction because of their almost negligible blood supply. He concluded this paper by stating that "no pulsation, however forcible, no thrill, however intense, no bruit, however loud, singly or together, justify the diagnosis of aneurysm of the abdominal aorta—only the presence of a palpable expansile tumour", and abnormal abdominal pulsation is common in neurotic and hysterical states, in the presence of abdominal tumours, in anæmia, and in aortic insufficiency.

While reading Osler's publications, one must realize that the medical clock has not stood still since Osler's day, or perhaps some of our older confrères might prefer to state that the medical pendulum has not ceased to swing. This is particularly true in the case of angina pectoris. Osler includes in his group of cases of angina, many which would not be included nowadays. We would agree with the opening statement,—

"Pain is one of the earliest and most constant symptoms in aneurysm of the aorta", but hardly with the title of the paper, in which this statement appears,—"*angina pectoris*, an early symptom in aneurysm of the aorta". It is doubtful if any cases described in this paper would now be diagnosed *angina pectoris*. One was a patient of the late Professor McPhedran, a man of 49, with a history of pains for years, in stomach and lower chest, worse at nights, not aggravated by excitement or exertion; no tracheal tug; nothing found in examining the heart, who yet, three and one-half years later, had an obvious aneurysm.

Most of Osler's publications were written with the purpose of instructing or teaching, and he used telling phrases most aptly, so that they tended to stick in the memory of his readers. For instance, in writing in *Modern Medicine*, on aneurysm, he quoted some unknown—"Venus loves the arteries". That is much more likely to be remembered than the bald statement that syphilis causes *mesaortitis*. Many teaching points are driven home in this treatise, e.g., "More mistakes are made by not looking than by not knowing", "Strip to the buff", "There is no disease more conducive to clinical humility than aneurysm of the aorta", "Inspect the back", "Look for unequal pupils", "Look for unilateral clubbing", "and unequal pulses", and he quotes Pirogoff, as follows,—"*There are in everyone's practice moments in which his vision is holden, so that even an experienced man cannot see what is, nevertheless, perfectly clear. At least I have noticed this in my practice. An overbearing self-confidence and preconceived opinion, rarely a weariness, are the causes of these astonishing mistakes*".

Osler's writings on aortic syphilis dealt almost exclusively with aneurysm of the aorta, yet he noted that syphilis caused, also, or alternatively, aortic insufficiency, and in a few instances he noted that it might markedly narrow the opening of the right or left coronary artery. He believed that most cases of *angina pectoris* result from coronary artery disease, and he also taught that syphilitic infiltration of the root of the aorta caused *angina pectoris*. It is doubtful, however, if he appreciated that syphilitic aortic disease probably only caused *angina pectoris* if it caused occlusion of the coronary orifices or aortic insufficiency, or both. I am, of course, referring to *angina pectoris* as it is now defined. In his *Lumleian* lectures on *angina pectoris*, in 1910, he again discussed the rôle of syphilis in *angina pectoris*, but of particular interest are the following statements in reference to aortic syphilis, namely, "When a man gets specific aortitis, it means he has not had efficient treatment", and, further, "There is nothing in the lesion of the arterial wall which mercury and iodide of potassium cannot control". This is interesting, in view of the present scepticism of some physicians regarding their ability to pre-

vent aortic syphilis by the early and vigorous use of arsenic, bismuth, etc. It would appear evident that aortic syphilis, in the form of fatal aneurysms in younger people, and especially in the form of large aneurysms, is becoming rarer, even allowing for present day less skilled clinical observation, (for which is often substituted fluoroscopy).

Osler stated that many cases of ruptured aneurysm became coroners' cases. This is not the case in Toronto, as three of the busiest coroners' pathologists were unable to recall a single case, while they had seen several cases of dissecting aneurysm, which of course is not syphilitic. This can be taken as evidence of the efficiency of modern public health measures.

It has been an education to follow Osler's accurate observations in the earlier days, before he ventured into clinical fields, through his painstaking routine examinations, skilful reasoning, and logical conclusions—all illuminated by apt quotations and striking commentaries. It has been interesting to follow him from the days of dry diets, bleeding, and potassium iodide, through the stages of various now discarded operative procedures, to his later days when he advocated the vigorous use of salvarsan, mercury, etc. Aortic syphilis is certainly one of the many fields ploughed, harrowed, cultivated, and made to yield fruitfully by that great master of modern medicine.

Association Notes

The Seventy-first Annual Meeting

Under the Chairmanship of the President-elect, Dr. Duncan Graham, of Toronto, the Central Program Committee is making excellent progress in developing plans for the forthcoming annual meeting to be held in Toronto during the week of June 17, 1940, in conjunction with the sixtieth annual meeting of the Ontario Division.

The personnel of the Committee is as follows: *Chairman*, Dr. Duncan Graham; *Drs.* Harvey Agnew, Alan Brown, Howard Burnham, W. J. Cryderman, H. K. Detweiler, H. A. Dixon, J. H. Elliott, J. G. Falconer, A. A. Fletcher, Roscoe Graham, Wallace Graham, E. B. Hardy, Kenneth M. Heard, E. S. Jeffrey, A. D. Kelly, R. C. Laird, F. S. Lazenby, H. W. B. Locke, J. C. McClelland, Alexander E. MacDonald, W. T. Noonan, F. B. Plewes, G. E. Richards, John Ross, T. C. Routley, William Scott, H. J. Shields, L. J. Siebert, F. F. Tisdall, Melville Watson, D. E. S. Wishart, Geo. S. Young.

It has been decided that the Round Table Conferences which were inaugurated at the Montreal meeting last year so successfully will be continued this year, taking place between the hours of nine and ten o'clock in the morning on Wednesday, Thursday and Friday.

General Sessions will be held on these three days from ten o'clock in the morning until half past twelve. On the afternoons of Wednesday, Thursday and Friday the various Sections will meet.

General Council will meet on Monday and Tuesday.

A change has been made in respect to the Golf Tournament, it being moved back from Friday to Tuesday.

The Annual General Meeting followed by the President's Reception and supper dance will take place on Wednesday night.

Thursday night has been given over to the Committee on Economics when an excellent program will be presented under the Chairmanship of Dr. Wallace Wilson, of Vancouver.

All the scientific sections are busily engaged in preparing their programs, details of which will be available in the near future.

At this juncture plans for the forthcoming meeting point to one of the most successful conventions in the Association's history.

T. C. ROUTLEY

Medical Military News

QUESTIONNAIRES

Herewith follows a report by provinces of the questionnaires *re* military service which have been returned to us:

British Columbia	762
Alberta	434
Saskatchewan	558
Manitoba	590
Ontario	3,918
Quebec	1,621
New Brunswick	261
Nova Scotia	373
Prince Edward Island ..	40
Total	8,557

The British Medical Association, in a similar survey, is able to report the receipt of completed questionnaires from well over 95 per cent of the profession. While we have received returns from something over 85 per cent it would be gratifying, indeed, if this percentage could be pushed up to 95 or better. The co-operation of all members of the profession is asked for in this desideratum.

CO-OPERATION

At its meeting in Ottawa on December 16th the Canadian Medical Advisory Committee was privileged to confer with Colonel Gorssline, Director General of Medical Services, on many matters of mutual interest and concern. The Committee assured Colonel Gorssline of the keen desire of the Canadian Medical Association to render the Department every possible co-operation and service. The D.G.M.S. expressed himself as very appreciative of our

proffered services. The relationship which has been established is indeed most cordial, and, from our point of view, we trust that we can prove to be helpful to the Department.

BLOOD TRANSFUSIONS

Under the Chairmanship of Dr. L. J. Rhea, of Montreal, a special committee has prepared and presented a most elaborate report on Blood Transfusions and allied problems, which report has been made available to the D.G.M.S.

ENLISTMENT FOR A LIMITED TIME

The Committee had before it the following resolution from the Advisory Committee of the British Columbia Division:

That this Committee strongly recommend to the C.M.A.C. that medical men be permitted to enlist for limited time service overseas, with the further suggestion that the period of time suggested be one year and that, at the expiration of that period, re-enlistment might be possible.

This question was discussed with the D.G.M.S. who stated that men could be recalled on reasonable grounds, but a general ruling could not be made applicable to all enlistments.

ARMY PAY

The Alberta Division presented a strong resolution supported by the Council of the College of Physicians and Surgeons of Alberta, pointing out that qualified medical men are a distinctive professional class necessary to an army because they are the only class of trained personnel who can perform the services required; and that their training has been acquired largely at their own expense and the army has made no contribution to this training; also that many capable and responsible medical men will hesitate to offer their services to the army if the pay and allowances of their rank will not permit of the discharge or even partial discharge of the civilian responsibilities which a medical man finds himself obliged to meet. The Alberta Division therefore, feels that the pay and rank of medical men in the army should be such as will meet the conditions set forth, in order that there may be an approach to equality in the matter. This was discussed with the D.G.M.S. who stated that the question of pay and allowances for medical men was under very careful consideration. The Department recognizes the problems involved, and the D.G.M.S. stated that everything possible would be done to treat the medical profession fairly.

VENEREAL DISEASE

On the invitation of the D.G.M.S., Drs. Frank S. Patch, of Montreal, and Robin Pearce, of Toronto, acting in a consultative capacity, have submitted to the Department a report on Venereal Disease in the army.

X-RAYS OF THE TROOPS

Excellent progress has been made in x-ray examination of the troops, with a very small

percentage of recruits having been dropped from the service because of disabilities found.

PHYSIOTHERAPY

The Canadian Physiotherapy Association advised the C.M.A.C. that it had offered its services to the Government in the present war, suggesting that at least two physiotherapists be appointed to base hospitals going overseas. To qualify for membership in the Canadian Physiotherapy Association, a candidate is required, after senior matriculation, to take a two-years' course at a university, followed by six months' service in a hospital. The Canadian Physiotherapy Association feels that their graduates, if they are to be used in base hospitals, should have a military status equivalent to a nursing sister.

After careful consideration it was agreed that we recommend to the D.G.M.S. that the appointment of physiotherapists to each base hospital be approved and that the standard of qualification for such appointments be membership in the Canadian Physiotherapy Association; and that, in the event of a physiotherapist so selected being a woman, she be given a rank equivalent to that of a nursing sister; and that a copy of this resolution be forwarded also to the Canadian Nurses Association.

CONFERENCE WITH THE DEPUTY MINISTER OF PENSIONS AND NATIONAL HEALTH

The Canadian Medical Advisory Committee had the pleasure of an hour's conference with the Deputy Minister of Pensions and National Health, when questions of War Veterans' Allowances, medical examination fees, doctors working on part time basis with the Department of Pensions and National Health, application of certain forms of treatment in the army, and medical association fees (both provincial and national) were discussed.

INFORMATION

Already information to be derived from the questionnaires has been asked for by Headquarters and by two of the Military Districts. Reference to the information tabulated in the questionnaires is readily available and has been furnished as requested.

CONCLUSION

Your committee continues to keep in close touch with the military authorities.

T. C. ROUTLEY

Since 1937 the following eminent Viennese doctors have been commemorated on postage stamps: Gerhard van Swieten (1700-1772), Leopold von Auenbrugger (1772-1809), Karl von Rokitansky (1804-1878), Joseph Skoda (1805-1887), Ferdinand von Hebra (1816-1887), Joseph Hyrtl (1810-1894), Theodor Billroth (1829-1894), and Theodor Meynert (1833-1892).

Medical Societies

The Canadian Physiological Society

The fifth annual meeting of the Canadian Physiological Society was held at Queen's University, Kingston, on November 3rd and 4th. There was an attendance of approximately 140.

The Council for 1939-40 was elected as follows: *President*, Prof. N. B. Taylor, University of Toronto; *Secretary*, Prof. G. H. Ettinger, Queen's University; *Treasurer*, Prof. E. M. Watson, University of Western Ontario; *Councillors*, Professors A. Barbeau, Université de Montréal; A. W. Downs, University of Alberta; E. W. McHenry, University of Toronto; V. H. K. Moorhouse, University of Manitoba; David Thomson, McGill University; and C. B. Weld, Dalhousie University.

Nineteen new members were elected, making a total membership of two hundred and forty. It was decided to hold the next meeting in Toronto early in November, 1940.

Professor Henderson reported for the Journal Committee that a survey had shown that more than seventeen hundred pages per annum are published from Canadian laboratories on medical research problems. The Committee feels that a journal should be started very soon. The Associate Committee on Medical Research of the National Research Council has expressed interest in a Canadian Medical Research Journal and asked the Society to formulate a plan for such a journal for its consideration.

The Journal Committee was enlarged under the chairmanship of Prof. C. H. Best, and instructed to proceed with the establishment of a journal as soon as financial arrangements could be made.

Sixty papers were read. Abstracts of some of these having a special medical interest are given below.

A copy of the Proceedings, containing abstracts of all papers, may be obtained from the Secretary, Dr. G. H. Ettinger, Queen's University, Kingston, Ont.

PROTECTION AGAINST EXPERIMENTAL ULCERS AND INHIBITION OF GASTRIC SECRETION BY SUBSTANCES IN URINE.—M. H. F. Friedman, D. J. Sandweiss, H. C. Saltzstein and A. Farbman, Wayne University College of Medicine and Harper Hospital, Detroit, Mich., U.S.A.

Evidence is presented that a substance may be extracted from the urine of normal pregnant and non-pregnant women which exerts a definite protection against experimental peptic ulcers in dogs (Mann-Williamson technique). This protective action is not shown by extracts of urine from patients with peptic ulcer. A study has been made to determine if this protection is the result of inhibition of gastric secretion. While extracts from normal urine but not peptic ulcer urine tend to prevent the formation of experimental ulcers, both types of urine markedly inhibit in dogs gastric secretion which has been stimulated by histamine. It would appear from this and other data to be presented

that the beneficial effect on experimental peptic ulcer is due to some factor in the urine other than the one responsible for the inhibition of gastric secretion. At present we are still uncertain about the organ or the mechanism of the body responsible for the elaboration of either the gastric secretory depressant or ulcer-protecting substances recoverable from normal urine.

A preliminary investigation of the possible therapeutic use of normal urine extracts in cases of peptic ulcer in man has been encouraging. However, the clinical results can be evaluated only by employing a larger series of cases and by a longer follow-up period.

THE HYPERTENSIVE EFFECT OF BLOOD FROM HYPERTENSIVE DOGS.—D. Y. Solandt, R. Nassim and C. R. Cowan, Departments of Physiology and Physiological Hygiene, University of Toronto.

Goldblatt (*J. Exper. Med.*, 1934, 59: 347) has shown that a partial occlusion of the renal arteries in dogs results in a marked and relatively permanent hypertension. Greenwood, Nassim and Taylor (*Canad. M. Ass. J.*, in press) has obtained the same result by removing one kidney and applying a collodion cast to the other kidney. Fasciolo and others (*J. Physiol.*, 1938, 94: 281) have demonstrated a vasoconstrictor substance in blood from the renal veins of animals treated by Goldblatt's technique. They have, however, been unable to demonstrate any vasoconstrictor substance in the systemic blood. Further, in experiments where cross circulation was maintained between a hypertensive and a normal or hepatectomized dog the blood pressure of the latter failed to rise (Katz and others, *Am. Heart J.*, 1938, 17: 334). In the present experiments cross circulation was effected through a double pump (Solandt and Robinson, *J. Sci. Inst.*, 1938, 15: 268) which prevented the blood pressure in one animal having any direct effect on the blood pressure in the other. The exchange was approximately 3 litres per hour in each direction. The exchange of blood between a hypertensive and a nephrectomized dog resulted in a rise in pressure in the nephrectomized animal. Exchange between a hypertensive and a normal animal resulted in no change in the blood pressure of the latter. In each case the blood pressure in the hypertensive dog was lowered. We conclude that the systemic blood in an animal suffering from experimental hypertension of renal origin contains some substance which can produce an immediate hypertensive response in another dog and that this substance is removed or inactivated by the kidneys.

SEASONAL VARIATION IN THE WATER CONTENT OF THE RESPIRATORY TRACT.—Grant McD. Johnston, Department of Pharmacology, Queen's University, Kingston.

This study was made as the ground work for investigation of expectorant action. It was found that at any given season the water content of the different parts of the respiratory tract of albino rats and guinea-pigs remains remarkably constant (Coefficient of Variation about 1). More detailed studies in albino rats revealed a sharp increase in water at the time of the first cold spell in the autumn and a prolonged decrease in mid-winter in animals housed in hot water heated quarters. The coincidence of these seasons with those in which respiratory tract infection is most common was noted.

THE EFFECTS OF CARDIO-SENSORY DENERVATION ON THE DEVELOPMENT OF VENTRICULAR FIBRILLATION FOLLOWING CORONARY ARTERY OCCLUSION IN CONSCIOUS ANIMALS.—C. G. McEachern, University of Toronto.

The incidence of fatal ventricular fibrillation following occlusion of the circumflex branch of the left coronary artery in the conscious dog is 60 per cent.

When the anterior descending branch of the left coronary artery is ligated in the conscious animal the incidence is 25 per cent. When the left circumflex branch is occluded following the unilateral removal of the stellate and upper five thoracic ganglia (sympathetic) the development of fatal ventricular fibrillation is reduced to 33 per cent. Bilateral removal of the stellate and upper five thoracic ganglia further reduces this incidence to less than 10 per cent. Bilateral removal of the stellate and upper five thoracic ganglia reduces the incidence from 25 to 0 per cent when the anterior descending branch is occluded.

Unilateral cardio-sensory denervation diminishes the pain following coronary artery occlusion. Bilateral cardio-sensory denervation of the heart eliminates the pain.

ACUTE HYPERTHYROIDISM ASSOCIATED WITH A SUPRASELLAR TUMOUR.—E. A. Linell, Department of Pathology and Bacteriology, University of Toronto.

A woman whose physical conformation suggested a slight degree of pituitary dwarfism was in good health until within a month of her death at the age of 39. She then rapidly developed a well defined clinical picture of hyperthyroidism with a basal metabolic rate rising to plus 62. A few hours following a subtotal thyroidectomy she became acutely ill with symptoms suggesting thyroid storm and died 14 hours after operation.

Post-mortem revealed a suprasellar tumour of congenital type compressing and invading the floor of the 3rd ventricle in the position of the tuberal hypothalamic nuclei. The involved areas of the hypothalamus were softened and contained massive terminal hæmorrhage. Microscopical examination showed recent and more chronic degenerative changes in the hypothalamic tissue, suggesting that the patient's terminal illness of sympathetic hyperactivity, manifested clinically by a typical picture of hyperthyroidism, was due to the changes in the hypothalamus caused by the tumour. It is of interest that the patient had symptoms and signs suggesting diabetes insipidus at the age of 33.

THE EFFECT OF TESTOSTERONE ON THE KIDNEY AND ON THE GENERAL CONDITION OF URÆMIC ANIMALS.—Hans Selye, Department of Anatomy, McGill University, Montreal.

Our previous investigations showed that in the mouse the kidney enlarges under the influence of testosterone propionate, progesterone or desoxycorticosterone (H. Selye, *J. of Urology*, 1939). Histologically such kidneys showed marked hypertrophy of the proximal and distal convoluted tubules without degenerative changes. It appeared possible that these hormones have a direct trophic influence on kidney tissue or else that they lead to such metabolic changes which would necessitate the increased excretion of waste products by the kidney. In this latter case, the kidney hypertrophy would merely be a compensatory phenomenon. In order to clarify this question, 18 female mice (Little's C57 black strain) have been divided into three groups of 6, the first group received 4 mg. of testosterone propionate daily in oil, and the second group the same amount of cholesterol over a period of ten days. On the eleventh day all these animals and the remaining 6 untreated controls were nephrectomized. The kidney weights in the cholesterol-treated and in the untreated controls were approximately the same, while the testosterone-treated animals showed a considerable increase in kidney weight. There was no difference in the length of survival between the normal and the cholesterol-treated animals, the average survival being 36 hrs. Contrary to expectations, the testosterone-treated animals survived longer than the controls, the average survival being approximately 48 hrs. At a time when both groups of controls were in deep uræmic coma, the testosterone-treated animals were still in good condition. These observations appear to be in contradiction

with the conception that the effect of testosterone on the kidney is due to metabolic changes necessitating increased renal activity.

The titles follow of other papers read at the meeting.

- THE RESTORATION OF NORMAL BLOOD PRESSURE IN EXPERIMENTAL CONDITIONS OF SHOCK.—M. H. F. Friedman.
- THE EFFECT OF A WIDE RANGE OF DOSES OF PITRESSIN AND PITOCIN ON THE BODY WATER OF ALBINO RATS.—N. D. Garand.
- VITAMIN B₆ AND FAT METABOLISM.—Gertrude Gavin and E. W. McHenry.
- BILATERAL SYNCHRONICITY OF ALPHA ACTIVITY IN MAN.—J. E. Goodwin.
- EFFECTS OF VARIOUS DRUGS ON THE DEVELOPMENT OF VENTRICULAR FIBRILLATION FOLLOWING CORONARY ARTERY OCCLUSION IN CONSCIOUS ANIMALS.—G. W. Manning.
- THE ROUTES OF ENTRY OF WATER INTO FROGS INJECTED WITH PITUITRIN.—A. E. Smith.
- CELLULAR ACTIVITY AT LOW OXYGEN TENSIONS.—J. A. Kitching.
- USE OF MULTILAYERS IN CHEMO-IMMUNOLOGICAL STUDIES.—G. A. Meek and W. R. Franks.
- RATE OF TURNOVER OF KIDNEY PHOSPHOLIPID.—R. G. Sinclair.
- THE EFFECT OF NATURAL AND SYNTHETIC PREPARATIONS IN K AVITAMINOSIS.—J. K. Souch, A. S. Cook, L. Lowenstein and J. Kaufmann.
- HEREDITARY JAUNDICE IN THE RAT.—Hilda Tait Malloy.
- THE EFFECTS OF CARDIO-SENSORY DENERVATION ON THE DEVELOPMENT OF VENTRICULAR FIBRILLATIONS FOLLOWING CORONARY ARTERY OCCLUSION IN CONSCIOUS ANIMALS.—C. G. McEachern.
- EFFECT ON THE THIRD STAGE OF LABOUR OF INJECTIONS OF ACETYLCHOLINE INTO THE UMBILICAL VEIN.—G. L. Bateman.
- THE TIME RELATIONS OF HEPARIN ACTION ON BLOOD CLOTTING AND PLATELET AGGLUTINATION.—C. H. Best and D. Y. Solandt.
- CHANGES IN THE BODY WATER OF FROGS PRODUCED BY STIMULATING THE EYES.—E. M. Boyd and F. M. Young.
- METABOLISM OF THE ISOLATED PERFUSED CAT'S BRAIN.—A. L. Chute and D. H. Smyth.
- THE EFFECT OF ANTICOAGULANTS ON THE PARTITION OF IODINE IN BLOOD.—Eleanor L. Clarke.
- OBSERVATIONS ON THE ADRENALECTOMIZED SYMPATHECTOMIZED DOG: A NEW PREPARATION.—R. A. Cleghorn and J. L. A. Fowler.
- CORNEAL CHANGES IN THE EYE OF THE CHICK EMBRYO PRODUCED BY SUPRARENAL CORTICAL SUBSTANCES AND PROGESTERONE.—A. J. Dalton, M. A. Sergeyeva and H. Selye.
- THE EFFECT OF THIAMINE CHLORIDE ON THE EXPOSED FROG HEART IN SITU.—R. W. Dingwall.
- THE TOXIC EFFECTS OF ESTROGENS AS INFLUENCED BY PROGESTERONE.—H. Selye and J. Stevenson.
- LA GLUCOSE COMME AGENT DE RESISTANCE A L'ASPHYXIE CHEZ OSTREA VIRGINICA.—Louis-Paul Dugal.
- ABSENCE OF CHOLINERGIC ACTION OF ESTROGENS ON PLACENTAS OF LABORATORY ANIMALS.—G. H. Ettinger, W. A. Young and G. G. S. Moulds.
- INFLUENCE OF DIET ON GLUCOSE ABSORPTION BY THE RAT.—R. J. Fassina and R. G. Sinclair.
- REFLEX AUGMENTATION OF RESPIRATION.—J. K. W. Ferguson.
- THE EFFECTS OF SODIUM, POTASSIUM AND CALCIUM ON THE AMPLITUDE OF CONTRACTION IN THE SKELETAL MUSCLE OF THE FROG.—John Fiddes.
- BLOOD AND URINE CHANGES OCCURRING IN ADRENAL INSUFFICIENCY IN ADRENALECTOMIZED SYMPATHECTOMIZED DOGS.—J. L. A. Fowler, R. A. Cleghorn, J. S. Wenzel and A. P. W. Clarke.
- INFLUENCE OF DIBENZANTHRECENE-PROTEIN CONJUGATES ON BODY WEIGHT.—W. R. Franks and M. M. Shaw.
- VARIATIONS IN CAPILLARY RESISTANCE UNDER PHYSIOLOGICAL CONDITIONS.—Rhoda Grant and C. B. Weld.
- NOTE ON THE ANÆSTHETIC CHARACTERISTICS OF METHYL ACETYLENE.—V. E. Henderson.
- CHRONICALLY AND ACUTELY DISORDERED BEHAVIOUR IN RATS.—G. Humphrey.
- SOME PHYSIOLOGICAL CHANGES PRECEDING SUDDEN DEATH IN EXPERIMENTAL ANIMALS.—J. M. Janes.
- THE CONJUGATION OF THE CARCINOGEN P-DIMETHYLAMINOAZOBENZENE WITH PROTEIN.—W. N. Keefe and W. R. Franks.
- CEREBRAL BIOELECTRIC POTENTIALS IN METRAZOL AND INSULIN SHOCK.—W. K. Kerr.
- THE GROWTH OF TROPHOBLAST TRANSPLANTED TO THE ANTERIOR CHAMBER OF THE RAT'S EYE.—B. Kropp.
- STUDIES ON RAT BRADYCARDIA.—D. G. H. MacDonald and E. W. McHenry.
- LIPIDS FROM TUBERCULOUS LUNGS.—L. B. Macpherson and J. T. Fallon.
- THE EFFECT OF ADRENALECTOMY ON THE BLOOD COUNT OF THE RAT.—G. Masson and A. J. Dalton.
- EFFECTS OF ESERINE, ACETYLCHOLINE AND ATROPINE ON THE ELECTRIC POTENTIALS OF THE CEREBRAL CORTEX.—F. R. Miller, G. W. Stavsky and G. A. Wootton.
- THE EFFECTS OF A LIVER FRACTION UPON FAT SYNTHESIS.—E. W. McHenry and Gertrude Gavin.
- A SCHEME FOR THE QUALITATIVE ANALYSIS OF URINARY CALCULI.—J. F. McIntosh and Ruth W. Salter.
- THE EFFECT OF ADRENALECTOMY UPON THE IMMUNOLOGICAL RESPONSE OF THE WHITE RAT TO DIPHTHERIA TOXOID.—G. A. McVicar and M. D. Orr.
- CHOLINESTERASE AND ELECTROLYTES.—B. Mendel and Dorothy Mundell.
- INFECTIVITY OF TUMOUR TISSUE AFTER VARIOUS PERIODS OF ANOXIA WITH GLUCOSE LACK.—G. J. Millar and W. R. Franks.
- SOME EFFECTS OF PROLONGED ADMINISTRATION OF DIETHYLSTILBESTROL TO RATS.—R. L. Noble.
- AN INK-RECORDING PEN FOR KYMOGRAPHIC REGISTRATION.—T. L. Patterson.
- CAPILLARY FRAGILITY IN SCORBUTIC GUINEA PIGS.—Helen M. Perry, Margaret Sheppard and E. W. McHenry.
- THE VARIATIONS IN THE VITAMIN A AND D POTENCY OF THE LIVER AND INTESTINAL OILS OF HALIBUT.—L. I. Pugsley.
- THE PHARMACOLOGICAL ACTIONS OF CULARINE.—A. K. Reynolds and R. A. Waud.
- BLOOD HISTAMINE IN ANAPHYLACTIC SHOCK IN THE RABBIT.—B. Rose.
- ON THE ANTAGONISM BETWEEN THE ACTIONS OF ADRENALINE AND ADRENAL CORTICAL EXTRACTS.—H. Selye, C. Dosne and A. J. Dalton.
- THE EXCRETION OF CORTIN FOLLOWING SURGICAL OPERATIONS.—P. G. Weil and J. S. L. Browne.
- THE PHASIC RESPONSE TO CORTICAL STIMULATION.—F. A. Mettler and E. A. Culler.
- STUDIES ON DOGS POISONED WITH SODIUM IODOACETATE.—J. S. Wenzel, J. L. A. Fowler and R. A. Cleghorn.
- SEASONAL VARIATION IN THE WATER CONTENT OF THE RESPIRATORY TRACT.—G. M. Johnston.
- BILATERAL SYNCHRONICITY OF ALPHA ACTIVITY IN MAN.—J. E. Goodwin.

Letters, Notes and Queries

The Repression of Culture and Science in Poland

To the Editor:

I consider it my duty to bring to your attention the official advice just received concerning the unprecedented act of violence committed by the German invaders on the representatives of Polish culture and science. This advice cannot be indifferent to the representatives of science and higher learning of the civilized world and particularly in countries bound with us by ties of sympathy and fellowship in arms.

The content of the advice is as follows. After many persecutions and outrages 160 professors of the University of Kraków were deported to a concentration camp in Germany and the university has been closed. The immediate cause was the refusal on the part of the professors to sign a proclamation which the Germans wanted to force upon them, and which was to contain the recognition of the legality of the German aggression and of the occupation of Poland. The fundamental reasons were the ruthless fight of the invaders against the Polish culture, the intention of forced germanization, and the fear of the student organizations. It is the first time that the University of Kraków, the oldest in Poland and one of the oldest in Europe, has been closed since its foundation in 1364. Similarly, were closed by Germans the Mining Academy in Kraków and the institutes of higher learning in Warsaw and Poznan, where a number of professors were also arrested.

May I add that, according to information received, some foreign universities or professors and student organizations started actions of protest at meetings and in the press, branding the crime against science.

Taking the liberty of bringing the above to your knowledge, I remain

Yours very truly,

DR. TADEUSZ BRZEZINSKI,

Consul of Poland

Montreal, Que.,

December 9, 1939.

Answers to letters appearing in this column should be sent to the Editor, 3640 University Street, Montreal.

A leech ought to have well cut clothes, dressing soberly and not like a clown or a poet. He ought too to have clean hands and well shaped nails which should not be black or filthy. He should behave courteously at a lord's dining table, and he should not offend the guests who are sitting near him either in words or in deeds. He should hear many things but speak little; the wise man says "It is better to use the ears than the tongue."—Master John of Arderne.

Topics of Current Interest

The Treatment of Anterior Poliomyelitis With Pooled Convalescent Serum

The following important memorandum emanating from the Ontario Department of Health is commended to the attention of our readers.

"It is difficult to assure sufficient in the way of evidence in support of the use of pooled convalescent serum in the treatment of anterior poliomyelitis to justify a continuance of the former practice of general gratuitous distribution. Until such time, however, as it is possible to impress the general public with the limitations of this type of treatment the department is prepared to continue a limited distribution of the serum.

"A copy of the recommendations of the committee set up by The Ontario Medical Association to estimate the merits of serum therapy and a copy of the recommendation of the Ontario Medical Association are as follows:

'A large number of reports on the use of convalescent serum have been reviewed. Those dealing only with the treatment of cases with serum and no controls do not prove anything for or against the serum. The best reports published embodying the value of therapeutic convalescent serum in the treatment of poliomyelitis show that serum does not decrease the incidence of paralysis or death as compared to control untreated cases. Dr. W. H. Park's figures from New York City are as follows:

Cases	Complete recovery	Paralysis and death
Controls.....	406 80.3%	19.6%
Convalescent serum	510 75.5%	23.1%

This report is the most significant from a statistical standpoint. Our own results in 1937 show the following:

	Paralysis
47 cases treated with 5% glucose	30%
45 cases treated with convalescent serum.....	28%

'As a result of these facts we do not feel the use of convalescent serum in the treatment of poliomyelitis has any effect on the prevention or development of paralysis and we feel that it is unnecessary to use convalescent serum in the treatment of poliomyelitis. The money spent on convalescent serum could be put to a much more useful purpose.'

"In connection with the report of the Special Committee on Poliomyelitis Convalescent Serum, the Secretary presented a recommendation from the Board of Directors to the effect that the attention of the Department of Health be drawn to the pronouncement of the Special Committee *re* Poliomyelitis Convalescent Serum, and that a recommendation be made to the Department of Health that the provision of the serum be discontinued in the Public Health

Laboratories. It was felt that, as long as it was available in the public health services, the public would consider it an essential procedure in the prevention and treatment of poliomyelitis.

"It was duly moved, seconded, and carried, that the recommendation from the Board be adopted."

The Health of Recruits in Britain

That a highly satisfactory state of health exists among young men aged 20 to 21 has been revealed by the medical examination of the first 20,000 of them called up for military service. Of these 20,000 no less than 84.5 per cent were classed in Grade 1, which means that they were found to be completely fit. Another 9 per cent were classed as fit except for minor disabilities such as will not impede their training; and a further 4 per cent were found to be suffering from disabilities such as defective vision or bad feet, but should be able to find places in the new Army where these disabilities would not constitute too great a handicap. Only 2.3 per cent of the men were found to be definitely unfit for military training.

These figures are gratifying enough by themselves, but they do not tell the whole story. For instance, the level of fitness does not vary very much in different parts of the country; and, again, the percentage of men completely fit in Scotland and the North of England, where acute unemployment has been prolonged, is stated to be 87, as compared with 82 per cent in the London area. Yet another point of importance is that these young men were born and spent the first few years of life when the country was enduring the last year of the war and its aftermath.

Comparisons are naturally being made between the figures already quoted and those obtained during the medical examination of recruits for the Regular Army, but it is pointed out that the two are not strictly comparable. Regular Army recruits are drawn from a much wider age group and are not to the same extent a sample of the whole nation. Nevertheless the difference between the rejection rates—32.4 per cent of Army recruits between the years 1926-36 and 2.3 per cent for young men in the first annual contingent of the Militia—is too great to be explained in any other way than the Minister of Health has done.

He has declared that the results of the medical examination of the militiamen are a striking tribute to the housing and other public health services and that the millions devoted every year to these social measures have not been wasted. They have resulted in the turning out of progressively healthier generations. Mr. Walter Elliot has further pointed out that these young men, born in 1918 and 1919, have not benefited from these services as much as those younger still, for the great developments of

pre-natal clinics and school-feeding—to mention only two—have taken place since their day, whilst the great drive against bad housing has been delivered only since some six years ago. The National Fitness movement and the growth of public interest in nutrition are still more recent. There is every reason to believe, therefore, that each year will show a progressive improvement in the results of the medical examination of annual contingents of militiamen. —*J. Roy. Inst. of Pub. Health and Hyg.*, 1939, 2: 397.

Abstracts from Current Literature

Medicine

A Study of the Incidence of Coronary Occlusion and Angina Pectoris in the White and Negro Races. Burch, G. E. and Voorhies, N. W.: *Am. J. M. Sc.*, 1939, 198: 685.

These authors found the incidence of coronary occlusion and angina pectoris to be quite high in the white as compared with the coloured population of Louisiana. During a 10-year period ending with 1937 there were 162 cases of coronary occlusion and 32 cases of angina pectoris admitted to the Charity Hospital of Louisiana. As regards coronary occlusion 138 (85.2 per cent) cases were white (121 males and 17 females), and 24 (14.8 per cent) were negro (22 males and 2 females). Of the 32 instances of angina pectoris 29 (90.7 per cent) were white and 3 (9.3 per cent) were negro. Correcting for the white to negro ratio of admission to the hospital, the incidence of coronary occlusion was found to be three and one-half times as great in whites as in negroes while the incidence of angina pectoris was four times as high. The authors are at a loss to explain these differences in incidence. They point to the fact that hypertension is more common in the negro than in the white population, a fact which would tend to minimize its importance as a predisposing factor in coronary occlusion and angina pectoris. High tension living conditions and occupations requiring a considerable degree of responsibility and intelligence are mentioned as possible factors bearing upon the relative frequency of these diseases in the two groups. E. S. MILLS

Exogenous Pernicious Anæmia. Alsted, G.: *Am. J. M. Sc.*, 1939, 197: 741.

Alsted reports the case of a man of 43 years who lived for seven years on a diet of bread, butter, cream, porridge and egg. This diet is deficient in vitamin B, calcium and phosphorus. He eventually developed a grave hyperchromic anæmia, with glossitis and lingual atrophy. Sternal puncture revealed marrow changes characteristic of pernicious anæmia. Free

hydrochloric acid was present in the gastric contents.

When the diet was increased to include adequate amounts of extrinsic factor in the form of liver extract devoid of the intrinsic factor he showed a typical remission ushered in by a reticulocyte rise and followed by a rapid restoration of all blood values. Subsequently the patient continued to improve on diet alone. The author believes that this case proves the existence of an exogenous form of pernicious anæmia. He believes that all stages exist between the purely exogenous irreversible form and that represented by the majority of pernicious anæmia patients. He emphasizes the importance of distinguishing between the two types, as the patients who suffer from the exogenous type may be spared from a lifelong treatment which is not only unnecessary but also troublesome and expensive. E. S. MILLS

Surgery

Pseudofracture of the Tibia. Roberts, S. M. and Vogt, E. C.: *J. Bone & Joint Surg.*, 1939, 21: 891.

Twelve of these interesting cases are reviewed. All of them have occurred in children between the ages of 4 and 16. The clinical signs have been tenderness over the sides of the proximal third of the tibiæ within a few inches of the epiphyseal line, local œdema, slight redness with increased skin temperature; occasionally there has been palpable periosteal thickening or increased leucocytosis. The etiological factors are unknown; in one case local trauma, in three preceding focal infections elsewhere. The x-rays have shown the signs of low-grade bone inflammation beginning as periosteal thickening which increases with a later break in the cortex which in some instances has progressed to complete simple fracture. Biopsy has shown cellular infiltration with fibrosis typical of chronic inflammation. The distinctive features are no history of sufficient trauma, development of fracture in 3 to 5 weeks after the onset, greatly increased amount of subperiosteal new-bone, the ability to be bilateral, and the recurrence after adequate treatment. The recommended treatment is plaster immobilization. One interesting point is the possibility that the condition is due to arrest of circulation in the nutrient artery.

FRANK DORRANCE

Single Large Cyst of the Lung Simulating a High-pressure Pneumothorax. Hudson, E. H.: *Brit. M. J.*, 1939, 1: 503.

A baby of 6 weeks suddenly screamed and struggled while nursing, became cyanotic, and then ashen cold and sweaty. A second attack occurred on the following day. After two weeks intermission he had another similar seizure, and at that time showed the classical

signs of right-sided pneumothorax. Careful x-ray study, however, pointed instead to the presence of an inflated lung cyst, probably in the middle lobe. Another quickly following congestive attack that was threatening life made it necessary to deflate the cyst by inserting a trocar and cannula into the fourth space just lateral to the nipple line. This gave instant and spectacular relief, which, however, was unfortunately followed by a pneumothorax through leakage of the cyst through the puncture. The cyst "blew up" again, and the child nearly died, again being relieved by withdrawal of the air, this time through a pneumothorax needle. Operative treatment was then undertaken, the chest being opened in the fourth interspace, when the cyst presented like a purple balloon. The cyst was sutured to the sides of the incision and a drainage tube sewn into it. A one-way valve was fitted. Infection supervened and death occurred after three weeks. A fragment of the cyst wall showed a columnar-celled lining. The danger of faulty diagnosis and treatment as for a pressure pneumothorax is pointed out. The ideal treatment is total removal of the cyst and even pneumonectomy. Fortunately such cases are rare. C. C. MACKLIN

Obstetrics and Gynecology

The Treatment of Hæmolytic Streptococcal Infections during Pregnancy and the Puerperium with Sulfanilamide and Immuno-transfusion. Chandler, C. A. and Janeway, C. A.: *Am. J. Obst. & Gyn.*, 1939, 38: 187.

In invasive streptococcal infections during pregnancy or the puerperium highly virulent organisms rapidly invade the tissues and ultimately enter the blood stream unless the infection is controlled before bacteriæmia occurs. Recovery in such cases occurs by the process of local fixation plus the development of immune bodies. In the treatment of these infections the chief weapons we possess are sulfanilamide, antibacterial antibody, and erythrocytic antitoxin. Although the action of sulfanilamide is still not known, its bacteriostatic effect on the hæmolytic streptococcus *in vitro* and *in vivo* has been demonstrated by innumerable investigators. Not all strains, however, are equally susceptible to the action of the drug; some are completely resistant (anaerobic strains especially) while others seem to require specific antibacterial antibody in addition to sulfanilamide for their destruction. Sulfanilamide and immune serum together have a greater bacterial effect *in vitro* on a virulent hæmolytic streptococcus than either alone.

Patients with profound toxæmia and an erythematous rash such as in puerperal scarlatina may be relieved of some of the symptoms by erythrocytic antitoxin.

Since it has been conclusively demonstrated that the source of infection in puerperal sepsis is

exogenous, the necessity for flawless aseptic technique in the delivery room is further emphasized.

A method of treatment of the streptococcal infections of pregnancy and the puerperium based on the most recent experimental observations on the hæmolytic streptococcus is presented. Laboratory methods for the rapid isolation and grouping of hæmolytic streptococci together with the technique of immunotransfusion are outlined.

ROSS MITCHELL

Recurrent Pregnancy Toxæmia. Kellar, R. J.: *J. Obst. & Gyn. Brit. Emp.*, 1939, 46: 462.

The author reviews the subject of pregnancy toxæmias from clinical and pathological facts. He states that pregnancy toxæmia and essential hypertension are in some way closely linked. Pregnancy toxæmia does not appear to be a cause of essential hypertension, yet 30 to 50 per cent of pregnancy toxæmias tend to manifest essential hypertension. In later life this is more marked. Pregnancy continued in hypertensive women tends to produce permanent hypertension; it hastens its development.

Pathological records of women dying months or years after a toxic pregnancy would seem to indicate that in the majority of cases death occurred from the effects of prolonged hypertension. One must not forget that a number of cases of recurrent toxæmia are due to latent glomerulo-nephritis.

P. J. KEARNS

Remote Prognosis of the Toxæmias of Pregnancy. Browne, F. J.: *J. Obst. & Gyn. Brit. Emp.*, 1939, 46: 443.

This study is based on 400 patients in 589 pregnancies followed for periods of twelve years to six months. The cases are grouped into pre-eclamptic toxæmias, eclamptics, hypertensives, chronic nephritis, and recurrent toxæmias. The residual lesion after pre-eclamptic toxæmia was invariably hypertension. Fifty decimal nine per cent of chronic nephritis cases did not follow hypertension. The residual lesion after eclampsia was also hypertension (60.8 per cent). Parity, length of illness, high blood pressure, and numerous fits all tended to a more marked residual hypertension than where the pre-eclampsia or eclampsia was sudden on onset and early relieved. Chronic nephritic patients do not bear pregnancy well (in 50 per cent of cases). Patients who develop residual hypertension after toxæmia usually have a familial history of hypertension and are not relieved of the hypertension between pregnancies.

P. J. KEARNS

Pædiatrics

Treatment of Burns and Scalds in Children. Dennison, W. M.: *The Lancet*, 1939, 2: 1107.

The modern treatment of burns and scalds dates from Davidson's introduction of the tannic acid treatment. The important principle of

Davidson's method is not tannic acid *per se* but coagulation. The present report discusses the results obtained with various coagulants. The following were tried: sodium carbonate tannic acid solution; gentian violet, silver nitrate, gallo-tannate of iron, ferric chloride and picric acid. No advantages were found in any of these over the following procedure which has become routine at the Royal Hospital for Sick Children, Glasgow.

With gauze moistened in warm saline all detached and blistered epidermis is removed and the underlying surfaces cleansed. A 1 per cent watery solution of gentian violet is then painted over the raw surface. This is dried with hot air from an electric hair drier. Gauze soaked in fresh 5 per cent solution of tannic acid is now applied and while still moist the area is covered with a 10 per cent solution of silver nitrate. The area is again dried by hot air and a further application of a 1 per cent solution of gentian violet is made. Later a cream of tannic acid, tragacanth and dettol is used for patching up cracks which appear in the coagulum. As regards prevention and treatment of toxæmia, minute care is taken to avoid moistening of the coagulum and the area is retanned if necessary. To support liver function a 10 per cent solution of dextrose is administered intravenously. Adrenal cortical extract (percorten) is given in doses of 5 mg. intramuscularly every 2 hours to combat an apparent suprarenal insufficiency in these cases. In the healing stage cod liver oil dressings have been used successfully. Results: in the past 5 years the total case mortality has been reduced from about 19 to 7 per cent, and the incidence of toxæmia and sepsis from 33 to 15 and 6 per cent, respectively. Cold tea has given a satisfactory coagulum in a series of cases and this is stated to be the best first aid remedy for use in the home.

REGINALD A. WILSON

Oto-rhino-laryngology

Some New Data Concerning the Pathology and Treatment of Ozæna. Halasz, G.: *J. Laryngol. & Otol.*, 1939, 54: 245.

The author first describes microscopical studies of ozæna which show inflammation and atrophy of the mucosa. He then discusses the pathogenesis of these conditions. Inflammation of the mucosa results from the lowered resistance to bacteria brought on by stasis. The atrophy results from trophoneurotic influences. The fundamental cause of these conditions he traces to impairment of tonsillar endocrine function. He believes that destruction or misdevelopment of the lymphatic tonsillar ring is the primary cause of ozæna. Ozænous subjects are likely to have atrophic tonsils, which condition he believes to be due to original hypoplasia. The author maintains that impaired secretion of some biohormonal specific damages the mucous mem-

brane of the upper respiratory tract, accounting for the exclusive appearance of ozæna in this region.

He expresses his main thesis thus. "*Hypoplasia of the tonsils and the adenoid tissue diminishes hormonal output, and lack of hormone becomes manifest as ozæna.*" However, if there is no disposition to the development of ozæna lack of tonsillar hormone will not produce it.

The author next discusses the nature of the tonsillar hormone. He finds it to be vaso-regulatory in function, choline-ergic in effect, and that it produces vasodilatatory stimulation of the nasal mucosa with perfect healing of the ozænous condition. Several choline-ergic properties have been demonstrated in tonsillar extracts, accounted for by the identification of acetylcholine as the active principle. Acetylcholine undergoes decomposition by a choline-esterase. By the inhibition of the action of choline-esterase obtained through the injection of physostigmine and potassium into the tonsil the author was able to prove that ozænous tonsils produce acetylcholine in sufficient amounts, but that this is decomposed by esterase before it is able to become effective.

Finally, he points out that successful treatment of ozæna has been achieved by means of intra-tonsillar injections of potassium and physostigmine which inhibit the action of choline-esterase.

E. A. STUART

Otitic Hydrocephalus. Asherson, N.: *J. Laryngol. & Otol.*, 1939, 54: 319.

N. Asherson describes otitic hydrocephalus, which Symonds defined as an acute internal hydrocephalus associated with acute or chronic suppuration in the middle ear or adnexa. He states this may be the sole intracranial complication present, or it may complicate an already diagnosed and treated intracranial complication, such as a lateral sinus thrombosis or a cerebellar abscess. He refers to two types and reports cases to illustrate each type.

Type 1 has no localizing signs, and is usually diagnosed tentatively and confirmed as the condition subsides. In producing symptoms of intermittent headache, vomiting, and continuous bilateral papilloedema it simulates the presence of a temporal lobe abscess or a cerebellar abscess. Its diagnosis is confirmed by a lumbar puncture, the pressure being raised to about 300 mm. of water. If the case is one of otitic hydrocephalus the cytology and chemistry of the fluid will be normal, whereas in the case of an intracranial abscess the cerebrospinal fluid is only very rarely normal.

Type 2 comes in association with an encephalitis of the temporal lobe, producing localizing neurological signs, and with an aseptic meningitis. It can be diagnosed only when a brain puncture has proved the absence of a temporal lobe abscess.

The author states that otitic hydrocephalus usually occurs before the age of 20. At its onset an infection of the ear is present, usually active. It may occur soon after an acute mastoiditis, and particularly after an operation for lateral sinus thrombosis, or mere obliteration of the lateral sinus with ligation of the internal jugular vein. Wasting is not, as with a cerebellar abscess, a feature. Drowsiness is not marked and the temperature and pulse are normal. The onset is sometimes delayed for as long as five months. The condition responds rapidly and completely to repeated lumbar punctures in from two to six weeks. The etiology is considered by most observers to be associated with sinus thrombosis and ligation of the internal jugular vein.

E. A. STUART

Radiology

The Radium Treatment of Angioma in Children.

Paterson, R. and Tod, M.: *Am. J. Roentgenol.*, 1939, 42: 726.

Three main methods of treatment have been tried, (a) surgical excision, (b) cauterization, and (c) irradiation. The object of this paper is to stress the fact that irradiation is a safe, certain method of curing these tumours, not a second resort to be attempted after CO₂ snow and other minor procedures have failed. It is justifiable to attempt the gamma-ray treatment of any angioma; there is no known satisfactory method of treating capillary types; the doses given do not harm, and if no response is obtained the attempt is abandoned. If there is any thickness of tumour tissue, this will be reduced and the discoloration will improve. The compact type responds well and the so-called "cavernous", really mixed, may completely disappear. The true cavernous angioma also does well, and blood spaces may be obliterated but the tortuous vessels usually remain, although with a much decreased blood content. The best time to treat is during infancy, from three months to two years.

The essentials of treatment are repeated low dosages of radium at correct intervals. The author suggests that these intervals be two months; usually three or more treatments are required. If dosage is carefully calculated and treatment is not continued indefinitely when it is obvious that a tumour of unusual resistance has been encountered a good cosmetic result without risk of damaging the skin may be expected.

R. C. BURR

The Anterior and Posterior "Notch" Shadows Seen in Lateral Roentgenograms of the Vertebrae of Infants. Wagoner, G. and Pendergrass, E. P.: *Am. J. Roentgenol. & Radium Therapy*, 1939, 42: 663.

In lateral roentgenograms of the vertebral bodies of infants there occur shadows which

would seem to indicate the presence of a "notch" or indentation in both the anterior and posterior walls of the bodies. In order to determine the cause of this notching the spinal column of a number of fetuses and newborn infants was examined.

The conclusions were as follows. (1) The posterior notch shadow results from the presence of an actual indentation in the posterior wall of the body. This indentation is present in all vertebrae and at all ages. The notch is the point of entrance and emergence of the posterior arteries and veins. (2) The anterior notch shadow results from the presence in this area of a large sinusoidal space within the vertebra. Indentation or notching of the anterior wall of the vertebral body is not present.

R. C. BURR

Therapeutics

On the Treatment of Raynaud's Disease with Papaverine Intravenously. Mulinos, M. G., Shulman, I. and Mufson, I.: *Am. J. M. Sc.*, 1939, 197: 793.

The authors have successfully treated 5 patients suffering from Raynaud's disease by means of histamine iontophoresis and papaverine intravenously. In Raynaud's disease the loss of circulation to the digits is due to closure of the digital artery in response to cold, the closure being due to smooth muscle spasm. The waxy pallor present in these patients during an acute attack is due to spasm of the minute vessels of the skin. Histamine iontophoresis releases this spasm, but histamine increases the spasm of the larger arteries. In order to counteract this latter effect of histamine papaverine is given intravenously. The treatment consists in the intravenous injection of papaverine hydrochloride three times weekly in doses of from 60 to 120 mg., usually before and after histamine iontophoresis. The treatments are continued for from 8 to 12 weeks.

The effects of this form of treatment are summarized as follows: (a) an objective increase in the vascular bed volume and the rate of blood inflow of the hand; (b) a complete alleviation of the syncope cyanoses and pain from exposure to cold; and (c) the healing of trophic lesions when these are present.

No addiction and little cerebral depression or other symptoms occur from the papaverine, despite long-continued treatment.

E. S. MILLS

The Use of Sulfapyridine in the Treatment of Gonococcal Urethritis in the Male. Johnson, S. H., III, Leberman, P. R. and Pepper, D. S.: *Am. J. M. Sc.*, 1939, 198: 594.

The authors followed 63 of 80 male patients suffering from gonococcal urethritis who were treated with sulfapyridine to determine if a complete cure resulted. The criteria of cure were normal, clinical and bacteriological findings

after (1) massage of the prostate and seminal vesicles, (2) passage of bougies and sounds with digital stripping of the anterior portion of the urethra, (3) consumption of alcoholic drinks, (4) sexual intercourse with a condom, (5) culture of the prostatic secretions.

Of the patients followed 54 had acute urethritis and of these 42, or 77.8 per cent were cured; 4 had subacute urethritis, with 100 per cent cured; 4 had chronic urethritis, all but one being cured. In 26 of the patients urethritis was of the anterior type, with 21 cures or 80.8 per cent, whereas in 37 with antero-posterior urethritis 29, or 78.4 per cent, were cured. The dosage of the drug employed was 3 gm. per day for 4 days then 2 gm. a day for 6 to 10 days.

Toxic reactions were observed in 45 patients (56.2 per cent). Usually these were mild and consisted of headache, nausea, weakness, dizziness, pruritus or substernal discomfort. More serious toxic reactions seldom occurred. Only 2 patients developed leucopenia, and two others, fever and chills. All toxic reactions subsided promptly on withdrawal of the drug and large fluid intake. As regards blood sulfapyridine levels the authors believe that such determinations are of doubtful value as they were unable to correlate the blood level with either the incidence of toxic reaction or the clinical response to the drug.

E. S. MILLS

An Investigation into the Treatment of Parkinsonism with Bulgarian Belladonna. Alcock, N. S. and Carmichael, E. A.: *Quart. J. Med.*, 1938, 7: 565.

The authors investigated the various drugs in common usage in the treatment of Parkinsonism, paying particular attention to extracts from plants of the belladonna group grown in Bulgaria. Equivalent doses of Bulgarian belladonna, English belladonna, stramonium, and trasentin were used. The claim that Bulgarian belladonna gives a more marked and lasting improvement could not be substantiated by the authors, who found little difference between Bulgarian and English belladonna, and, moreover, found that some form of stramonium gave the greatest improvement in most of the cases.

T. STEWART PERRETT

Pathology and Experimental Medicine

K Avitaminosis in Infants as Cause of Hemorrhagic Diathesis. Dam, H., Tage-Hansen, E. and Plum, P.: *Ugeskrift for Læger.*, 1939, 101: 896.

The authors state that in normal children a K avitaminosis, usually moderate, develops in the first days after birth and usually disappears after a week. This K avitaminosis causes a hypoprothrombinemia which must be regarded as the cause of the common slight hemorrhagic dia-

thesis in the newborn. Whether or not jaundice is present seems to be without significance. The avitaminosis seems to be due to a deficient supply of vitamin K throughout the intestine. In some cases of icterus gravis of the newborn, anaemia of the newborn, and congenital dropsy considerable hypoprothrombinæmia was established. Since the administration of K in two of their cases was followed by a rapid rise in prothrombin the authors conclude that there was a K avitaminosis in these cases. A complete lack of prothrombin established as early as 24 hours after birth is ascribed to reasons other than deficient resorption from the intestine. S. R. TOWNSEND

Disturbance in Coagulation of Blood in Jaundice due to Obstruction and its Treatment by Vitamin K. Koller, F. and Wuhrmann, F.: *Klin. Wchnschr.*, 1939, 18: 1058.

The authors show that the hæmorrhagic tendency in obstructive jaundice has found an explanation. The favourable therapeutic effect of vitamin K corroborates the assumption that a K avitaminosis exists. This is not surprising when it is considered that vitamin K is fat-soluble and that fat resorption is impaired in obstructive jaundice. After reviewing the clinical history in one case in which vitamin K exerted a specific effect the authors state that they were able to demonstrate the prompt action of vitamin K on the coagulation time and on the hæmorrhagic diathesis in nine cases of obstructive jaundice and four cases of carcinoma of the pancreas. They also state that analogous observations were reported by Danish and American authors. In hepatocellular icterus, especially cirrhosis of the liver, vitamin K seems to exert no effect, which suggests that the regenerating action of vitamin K on prothrombin presupposes a more or less intact function of the hepatic cells. However, the retardation in the coagulation which is observed in non-tropical sprue can be promptly counteracted by vitamin K. In this connection the authors direct attention to the fact that Fanconi ascertained in 1928 that in infantile sprue (intestinal infantilism) a form of hæmorrhagic diathesis occurs in which C avitaminosis does not appear but in which a hypoprothrombinæmia exists. The K avitaminosis in non-tropical sprue is understandable when it is considered that a disturbance in resorption is an essential factor in this disease.

S. R. TOWNSEND

Hygiene and Public Health

American Women Getting Thinner. *Stat. Bull., Metrop. Life Ins.*, 1939, 20: 1.

A good deal of publicity has been given in recent years to the danger of overweight. This publicity has been based on the experience of insurance companies and other organizations, which shows an excessive mortality among over-

weight persons. Fashion, so far as women are concerned, has also changed and habits too. Whichever cause has been responsible it is a fact, apparently, that women have gotten thinner. The records of the Metropolitan Life Insurance Company (ordinary department) show this quite definitely. At all ages and at all heights, with few exceptions, a decline in weight is shown in the years 1932 to 1934 as compared with the years 1922 and 1923. For the various age and height groupings the average weight losses run from one to nine pounds. FRANK G. PEDLEY

Studies in Chemotherapy, XI. Antibacterial Action of Phosphorus Compounds. Preliminary Report. Bauer, H. and Rosenthal, M.: *Public Health Reports*, 1939, 54: 2093.

Sulphur is not essential to chemotherapeutic action. Compounds active against streptococci have been obtained in which the sulphur was replaced by arsenic. These compounds are highly toxic, however. The present report deals with analogous phosphorus compounds which have a low toxicity. Three salts were used—sodium 4-dimethylaminophenyl phosphonous acid, tris(4-dimethylaminophenyl) phosphine, and bis(4-dimethylaminophenyl) phosphinous acid. The first two compounds were inactive although of low toxicity (8 and 4 grams per kilo respectively). The third compound (bis-phosphinous acid) had a higher toxicity (2 grams per kilo), but was active against streptococcal infections in mice, but less active against pneumococcal infection. The activity was equal to that of sulfanilamide. Related compounds are being studied. FRANK G. PEDLEY

Obituaries

Colonel Kenneth Cameron, C.M.G., V.D., M.D., C.M., of Montreal, died on December 25, 1939, at the Western Division of the Montreal General Hospital after being in indifferent health for some months. He became alarmingly ill whilst at the house of one of his friends, and succumbed within a few hours. He was in his 77th year.

A surgeon by profession, Colonel Cameron had always managed to follow a high family tradition of military service. He was the son of Archibald Cameron, of Toronto, and his grandfather was Lieut.-Col. Duncan Cameron, C.B., of the 79th Foot and Cameron Highlanders, who fought at the Battle of Waterloo. His mother, Agnes Margaret Barwick, was the daughter of Major James Barwick, also of the 79th Foot, and this regiment had been raised in 1793 by a kinsman, Lieut.-General Sir Alan Cameron, K.C.B., of Erracht. Many of the officers of the Cameron Highlanders were relatives of the original commanding officer and of Colonel Cameron. At the time of his death he was engaged in compiling a history of the families of the Camerons of Erracht, Clunes, Camisky and Lindally, who had one of the most distinguished records in the service of the British Army.

Colonel Cameron was born at Hamilton, Ont., on August 1, 1863. He was educated at Trinity College School, Port Hope, whence he came to McGill Uni-

versity and took his B.A. degree in 1884, winning the Logan Gold Medal and gaining first class honours. He graduated in medicine in 1887, with high honours, and became an assistant surgeon on the staff of the Montreal General Hospital in 1894, retaining this connection until 1918. He was also a member of the teaching staff in surgery at McGill University from 1896 to 1914, and found time to act on the editorial staff of the *Montreal Medical Journal*.

He began his military duties early in his career. In 1899 he was surgeon lieutenant with the Duke of York's Royal Canadian Hussars, and was transferred to the Army Medical Corps, on its organization, as lieutenant of No. 3 Bearer Company, on March 1, 1900. His devotion to this work never lessened and he rose steadily in military rank, being appointed lieutenant-colonel in 1907. He commanded No. 5 Field Ambulance from February, 1906, until September, 1910, and his work with this unit had much to do with bringing it up to the high state of efficiency which it displayed when war broke out in 1914.

At this time Colonel Cameron was D.A.D.M.S. of M.D. No. 4. He went overseas in October, 1914, with the First Contingent, as second in command (later O.C.) of the Surgical Division of No. 1 Canadian General Hospital, remaining with that unit until February, 1916, when he was appointed O.C. of No. 2 Canadian General Hospital at Treport. He became a full colonel on December 5, 1916. He returned to England in 1917, and acted as A.D.M.S. of the Bramshot Area until July, 1918, when he returned to Canada.

He was O.C. at Ste. Anne's Military Hospital from August, 1918, to April, 1920, and was demobilized to the Reserve in April, 1920. Subsequently he served as D.M.O. of M.D. 4 from 1921 to October, 1924, and at various intervals thereafter, going on the retired list on November 1, 1929.

His brilliant services overseas received fitting recognition in his being awarded the C.M.G. in 1918, being invested with this in the usual way by the King at Buckingham Palace. He was mentioned in dispatches on two occasions (1915 and 1917), and was also brought to the attention of the Secretary of State for War for valuable services rendered.

Dr. Cameron did not allow his other duties to distract him from his professional work; he was held in high esteem in his practice for his skill and gentleness of manner. He was president of the Montreal Medico-Chirurgical Society in 1920-21, and became a Fellow of the American College of Surgeons in 1912. About two years before his death he had completed a laborious and valuable work in the "History of No. 1 Canadian General Hospital".

Dr. Cameron was unmarried. He is survived by his brother, Hugh Cameron, of Toronto, and a number of cousins, of whom Archibald Howard lives in Montreal. Another brother, Donald, was killed in action in the Great War. He served with the Princess Pats. A third brother, Duncan, died recently in the west.

Dr. Theophile D. Boulanger, of Montreal, died on December 30, 1939. He was born in 1876 and a graduate of Laval University, Quebec (1898).

Dr. Harry Clifton Burgess, of Montreal, died on January 1, 1940, in his fifty-seventh year. A native of Sheffield Mills, N.S., the son of the late Stephen and Caroline Burgess. Dr. Burgess graduated from McGill University as M.D., C.M., in 1905, and became an intern for four years at the Royal Victoria Hospital and subsequently at the Johns Hopkins Hospital, Baltimore. Later he became medical superintendent of the Montreal Maternity Hospital, which post he held for two years. He did post-graduate work in London, Vienna and Berlin. He was appointed demonstrator in obstetrics and gynaecology at McGill University in 1912, and two years later was named lecturer in these subjects.

In 1912 he was also appointed assistant gynaecologist at the Royal Victoria Hospital and was holding this position when the Great War began. Dr. Burgess joined the staff of No. 3 General Hospital with the rank of captain, serving in this McGill unit under Col. H. S. Birkett. In December, 1916, he was promoted to major and was appointed chief surgeon to No. 3 Canadian Casualty Clearing Station, with which he served during the battles of Messines and Passchendaele. On returning home in March, 1918, he was principal medical officer of a large transport conveying troops back to Canada.

He resumed his association with the Royal Victoria Hospital as obstetrician and gynaecologist, and also as lecturer at McGill University, holding these positions until his death. He was regarded by his fellow practitioners as one of the ablest of clinical surgeons and an extremely good teacher.

Dr. Burgess was a member of the Canadian Medical Association, the Montreal Medico-Chirurgical Society, the American Gynaecological Society, a Charter Fellow of the American College of Surgeons, and a member of the Gynaecological Travel Club of America. He was the author of several publications dealing with that branch in which he specialized.

Dr. Michael Charles Burke, of High River, Alta., passed away on his 51st birthday, January 1, 1940, from heart failure. He was a graduate in medicine from the University of Manitoba (1915) when he joined the forces and went to Britain. On his return he registered in Alberta and established a practice in Blackie. Eight years later he went to Vulcan, but afterwards returned to Blackie on the solicitation of the people of the district. In 1937 he moved to High River.

Dr. Hubert Haldane Lee Castleman, of Chester-ville, Ont., died on October 2, 1939, aged forty-seven years. He was a graduate of McGill University (1920).

Dr. Louis David Chapman, of Windsor, Ont., died on October 17, 1939, aged fifty-eight. He was a graduate of the University of Western Ontario (1915).

Dr. William Richard Coles, of Regina, Sask., died on December 16, 1939. He was born in Prince Edward Island in 1872, the birthplace of his parents, and received his early education in the public schools of Prince Edward Island. Later he entered Trinity Medical School in Toronto, graduating in 1901. He returned to his native province to practise medicine at Murray River, and two years later came to Regina.

Dr. Coles' military experience began as a member of the militia artillery at Charlottetown, P.E.I., and in 1909 he was commissioned in the Royal Canadian Army Medical Corps. In 1916 he volunteered for service and went to France as medical officer with the 195th Battalion. For four of the 15 months he spent in France he was on duty with the Fourth Canadian Field Ambulance Corps.

He returned to Canada and in 1919 was discharged from the army. He resumed his private practice, but with the rank of lieutenant-colonel continued to command a medical unit connected with Military District 12.

Dr. William Henry Killeavy Crehan, of Stratford, Ont., died on January 11, 1940. Dr. Crehan was born in Wallacetown, Ont., October 6, 1890, son of the late Mr. and Mrs. William C. Crehan. His early education was received in the community of his birth and later he went to the high school at Dutton. He attended the Faculty of Education at Queen's University, Kingston, and then taught high school for six years.

About the time he was ready to prepare himself for the medical profession he altered his plans and offered his services in the Great War. Going to England, he joined the Imperial Army and served in

France for two years, from 1916 to 1918, as a lieutenant with the Royal Field Artillery.

With the signing of the armistice Dr. Crehan was once more able to pursue his goal, and graduated in medicine at University of Toronto in 1921. A short time later the young medical man came to Stratford to practise in association with Dr. G. R. Deacon, later opening an office of his own.

Dr. Charles Francis Crutchlow, of Montreal, closely associated for a number of years with the Montreal Rotary Club and the founder of the Westmount Rotary Club, died suddenly on December 21, 1939. He was in his 67th year.

Born in Montreal and educated in local schools, he was a graduate of Bishop's College, Lennoxville, obtaining his medical degree from that college in 1906, the year before its medical department was amalgamated with McGill University.

After practising medicine in Montreal for a number of years, he joined the staff of the Canada Life Assurance Company with which he had been associated for more than 35 years.

Dr. Thomas Vanston Curtin, of Vancouver, B.C., died on November 9, 1939. He was a graduate of Queen's University, Kingston (1901).

Dr. François Louis Demers, of Montreal, died on December 26, 1939, aged fifty-seven. He was a member of the Montreal City Council from 1932 to 1934. Afterwards he became a member of the medical staff of the city health department.

A native of St. Norbert, he took his B.A. degree with the Reverend Fathers of the Holy Cross at Memramcook, N.B., and graduated in medicine from Laval University in Montreal in 1909. He served his internship in the Hotel-Dieu and was later consulting physician to the Bruchesi Institute and the Sisters of Providence dispensary. He served during the Great War as captain in the Army Medical Corps, attached to Laval Hospital No. 6.

Dr. B. H. Dougan, Harvey Station, N.B., died on January 1, 1940, in the Victoria Public Hospital, Fredericton, N.B. He had suffered a fractured spine and other injuries in an automobile accident in September.

Dr. Dougan was born at New Jerusalem, and educated in public schools in New Brunswick. He graduated in medicine from McGill University in 1905. Dr. Dougan had always been active in public life, serving on the York County Council for seventeen years, and having sat in the Legislature at Fredericton from 1928 to 1935. He had been a coroner for many years. He is survived by his wife and two sons, Dr. Travis S. Dougan, of Harvey Station, and Alfred A. Dougan, a medical student at McGill University.

Dr. Charles Albert Drummond, of Conquest, Sask., died in December, 1939. He was born in 1867, and a graduate of Trinity University, Toronto (1895).

Dr. Edith Hamilton Gordon, of Toronto, died on December 17, 1939, in her fifty-fifth year. She was the first woman physician in Canada to obtain the degree of Doctor of Public Health. Born in Toronto, Dr. Gordon was the daughter of H. B. Gordon and the late Mary Reynolds Gordon. She received her early education in the Toronto schools and Westminster College. Following her graduation in Arts from the University of Toronto in 1909 she spent a year in Europe. In 1915 she received her degree of M.B. from the University of Toronto. She served for a year at Philipsburg Hospital, Penn., and from 1917 to 1918 was assistant medical adviser for women at Cornell University, Ithaca, N.Y. In 1920 she graduated from the University of Pennsylvania with the degree of Doctor of Public Health, and was appointed medical adviser to women at University of Toronto.

During her term of service with the Philipsburg Hospital Dr. Gordon established the pathological department. Although appointed assistant medical adviser for women at Cornell University, she assumed full charge when the adviser was called upon for war-time service in the last war.

Dr. Gordon was a member of the Academy of Medicine, Toronto; the Ontario and Canadian Medical Associations, the Canadian Public Health Association, American Public Health Association, the Laennec Association, University Women's Club and Ladies' Golf and Tennis Club. She was on the staff of the Out-door Chest Clinic of the Western Hospital.

Dr. Archibald Duncan Graham, of Bothwell, Ont., died on December 9, 1939. He was born in 1860 and a graduate of Trinity University, Toronto (1887). Dr. Graham was Medical Officer of Health for Bothwell and the township during his entire life there, and a former mayor. He was responsible for many progressive moves. Born in Lobo, he was educated in the collegiate institutes of Strathroy and St. Catharines and later attended Trinity Medical College, Toronto. Following his graduation he did post-graduate work and took further degrees in London and Edinburgh.

Dr. Allan Graham Hurdman, of Ottawa, died on December 11, 1939. He was born in 1877 and a graduate of Queen's University, Kingston (1901).

Dr. Yves Lefebvre, of Verdun, Que., died on December 20, 1939, aged forty-one. Dr. Lefebvre was director of the dermatology division of the Verdun General Hospital. For a number of years he was secretary of the West-End Medical Association. He was also secretary of the Medical Bureau of the Verdun General Hospital. He was a graduate of the University of Montreal (1924).

Dr. Dan MacDougall died suddenly in the Winnipeg General Hospital on December 22, 1939, at the age of 45. Born in Russell, Ont., he came to Winnipeg 26 years ago, and graduated from the Manitoba Medical College in 1917. On graduating he joined the C.A.M.C. and proceeded to England, returning to Winnipeg in 1919.

Dr. Thomas Brown McDonald, of Toronto, died on January 5, 1940, in his seventieth year. Dr. McDonald was the son of Mr. and Mrs. John S. McDonald, early settlers in Bruce County. He received his education in local schools and graduated from the University of Toronto in 1898. He practised for a time in Michigan and later in Maryfield, Saskatchewan, before coming to Toronto.

Dr. Louis George Pinault, of Campbellton, N.B., died on January 8, 1940. Dr. Pinault was a native of Rimouski, Que., and was born in 1873. He was educated at Rimouski Seminary and at Laval University, Quebec (M.D., 1898). Dr. Pinault had practised in Campbellton since 1900. He assumed much responsibility in community affairs, particularly in hospital matters, playing an important part in the building up of the local Hotel Dieu Hospital. He was an active member of the New Brunswick Medical Society; Canadian Medical Association and the American College of Surgeons and the Royal College of Surgeons of Canada; a charter member of the local Council of the Knights of Columbus. Dr. Pinault was a surgeon of note and was a pleasing example of the bilingual physician, equally at home in English or French, either in discussing a medical paper or in relating humorous anecdotes.

Dr. John Raper, of Bashaw, Alta., passed away December 29, 1939. Taken ill while driving his car, he expired a few moments later in his home. He was a man of high scholarship, having taken his degrees of B.Sc. and M.A. from Durham University, England. Later, he was ordained to the Anglican ministry and served as

rector in England for nine years. He came to Canada in 1913, a year later joining the forces, and went to the Great War. On his return he decided to study medicine and graduated from the University of Manitoba in 1924. Dr. Raper registered in Manitoba, but soon came to Alberta, where he practised in Holden for a short time, later going to Delburne, and finally settling in Bashaw.

Dr. John Boyle Travers, of Saint John, N.B., died on January 11, 1940, after a long life of usefulness to his province and a life filled with professional friendships. Dr. Travers was born in Saint John on November 15, 1864. He graduated from McGill University (1897), after which he practised medicine in Saint John for a short time and then began a life-long work in the Provincial Hospital, caring for the mentally ill. He was assistant Superintendent of the Hospital for 37 years. He retired from this position five years ago. Dr. Travers was an interested member of the Saint John Medical Society and also of the New Brunswick Medical Association. His viewpoint was always fresh and he was known to a multitude of friends for his kindness and cheerfulness.

Dr. Walter Clifford Whittaker, of Burnaby, B.C., died on May 24, 1939. He was born in 1872 and a graduate of Queen's University, Kingston (1895).

News Items

Alberta

The elections to the Council for the two-year period of 1940-41 resulted as follows: District No. 1, Medicine Hat, Dr. W. G. Anderson, Wardlaw; District No. 3, Banff-Red Deer, Dr. R. Parsons, Red Deer; District No. 5, Peace River, Dr. A. E. Archer, Lamont; District No. 7, Edmonton, Dr. W. A. Wilson, Edmonton; District No. 2, Lethbridge, Dr. A. Cherry, Lethbridge. Dr. Cherry was elected to fill out the term 1940 of Dr. J. K. Mulloy, who has removed from the district.

Hays Municipality voted to engage a municipal doctor, and the Council is looking to supplement the wishes of the people. It is interesting to note, however, that the village of Delburne, where the municipal office is located, has 89 ratepayers but defeated the by-law by casting only 29 votes all told.

The annual meeting of the Council is called for January 23rd in Edmonton, at which time the plans for the future will be considered.

There will be a meeting with the Chairman of the above Board, as at the present time the Medical Aid Fund is not sufficient to meet expenses. While the Board does not wish to raise the assessments, the members of the medical profession are opposed to a reduction of fees for services.

G. E. LEARMONTH

British Columbia

Dr. G. F. Amyot has recently been appointed Provincial Medical Health Officer in the place of Dr. H. E. Young, recently deceased. Dr. Amyot is widely known in British Columbia where he has filled several important positions in the Provincial Health Department and has been a trusted advisor of the Government. He has been away from the Province for some time engaged in special work in the United States.

A lectureship has recently been established by the Vancouver Medical Association, known as the John Mawer Pearson Lectureship, in memory of Dr. J. M. Pearson, one of the founders of the Vancouver Medical Association and former Editor of the Association Bulletin. In view of Dr. Pearson's particular interest in

Internal Medicine, lectures will be given on some phase of this specialty. A fund has been established, the interest from which will be used to defray expenses.

A new hospital is, we understand, to be erected in Penticton. Dr. A. K. Haywood, Superintendent of the Vancouver General Hospital and Mr. H. Whittaker, Provincial Architect, have been consulted as to the site and plans of this hospital. It is of interest, from an economic point of view, that in many parts of British Columbia the establishment of hospital schemes has been very successful in leading to improvements in financing of existing hospitals and to plans for enlarging some of these and developing new ones.

The first Medical Officer of the R.C.A.M.C. to leave for Overseas service from British Columbia was Lieut. H. A. Robertson, Medical Officer of the 72nd Battalion of the Seaforth Highlanders of Canada, who left with his regiment for an "unknown destination" on December 15th.

The campaign being conducted by the British Columbia Medical Association for increased membership in the Canadian Medical Association is beginning to show results and we are hopeful that before long a definite increase in members from this Province will be recorded.

J. H. MACDERMOT

Manitoba

On December 5th the Directors of the Medical Arts Building, Winnipeg, gave a dinner in honour of the tenants of the Building, 13 in all, who are on His Majesty's Service. The chair was taken by Dr. C. A. MacKenzie. The guests included Brigadier B. W. Browne and Lt.-Col. Williams, principal Medical Officer of M.D. 10. Mr. L. W. Brockington, K.C., proposed the toast to the doctors and dentists in uniform. He mentioned in particular "King Arthur" (Lt.-Col. Lennox Arthur) and his Knights of the Table Round, and also "Right-Way Corrigan" (Capt. C. E. Corrigan, M.O. Cameron Highlanders).

Dr. O. J. Day has been appointed part-time medical officer under the Winnipeg Health Department. His particular duties will be to supervise the health of pre-school children and to arrange for preventive inoculation.

A tribute to five physicians who have recently retired from the Honorary Attending Staff of the Winnipeg General Hospital was paid by the President of the University of Manitoba, members of the Board of Governors of the Hospital, and members of the Attending Staff at a dinner in the Manitoba Club on December 16th. Dr. John M. McEachern was chairman of the dinner, and the five doctors honoured were C. R. Gilmore, J. A. Gunn, W. A. Gardiner, D. S. MacKay, and A. Leishman.

Dr. N. J. Minish has been appointed by the Sanatorium Board of Manitoba to take charge of the newly equipped federal hospital for tuberculous Indians. By virtue of his wide experience in tuberculosis Dr. Minish is well fitted for the position. Dynevor Hospital is beautifully situated on the Red river about three miles north of Selkirk. The main building was formerly the rectory of St. Peter's Church. After the death of Archdeacon Cowley the Anglican church used this and another building as a hospital for Indians. Recently the Federal Government acquired the property and put it under the control of the Sanatorium Board of Manitoba. A new sanatorium for Indians is under construction at Fisher River, Manitoba.

After a seven weeks' tour of Indian medical services in western Canada Dr. Percy E. Moore, Assistant Superintendent of Medical Services, Indian Affairs Branch, Department of Mines and Resources, Ottawa, announced

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(1) Dick, Geo. F.: The Yearbook of General Medicine 1939, p. 92. (The Yearbook Publishers Inc., Chicago).

(2) Kendrick, P., and Eldering, G.: Am. J. Hyg., Sect. B, 29:133 (May) 1939.

(3) Sauer, R. W.: J.A.M.A. 112:305 (Jan. 28) 1939.



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that much progress has been made in improving the health of Indians in the west.

Dr. Murray Campbell has been appointed to the staff of the Manitoba Sanatorium, Ninette. ROSS MITCHELL

New Brunswick

Dr. H. A. Farris was re-elected President of the Saint John Tuberculosis Association on December 12, 1939.

Dr. L. E. German, of Campbellton, N.B., is rapidly recovering from injuries he received recently in a car accident.

Mental Hygiene Service in New Brunswick.—Establishment of a mental hygiene service for the Province of New Brunswick was announced in July, 1939, by Hon. Dr. F. H. Laporte, Minister of Health and Labour. The first visible evidence of this development has been the appointment of Dr. Arthur F. Chaisson to the staff of the Provincial Hospital in Saint John. In co-operation with Dr. E. C. Menzies, superintendent, a comprehensive program will be built up which, the Minister believes, will ultimately provide New Brunswick with an adequate mental hygiene service which will embrace the needs of the mentally deficient.

Dr. Chaisson is a son of Angus A. Chaisson of Saint John. He received his early education in the Saint John schools. In 1924 he received his Bachelor of Science degree from St. Francis Xavier University and his Master of Arts degree the following year. In 1925 and 1926 he was Lecturer in Biology at his University. From 1926 to 1929 he attended Harvard Graduate School, specializing in psychology, mental hygiene and education. Following this he was for five years Associate Professor of Education at St. Francis Xavier.

In 1934 he entered McGill University Medical School, graduating with the degrees of M.D., C.M. in 1938, and for a year had been an intern in the Royal Victoria Hospital. During his post-graduate study at Harvard he did clinical work at the Fernald State School for the Mentally Deficient at Waverly, Mass., which included mental testing and examination, social problems of feeble mindedness, institutional care, management and education of the feeble-minded.

A. STANLEY KIRKLAND

Nova Scotia

Dr. John W. MacIntosh, of Halifax, (Dal., '22) has been elected to fellowship in the American College of Physicians.

Dr. T. Earle Grant (Dal., '36) has left Port Hood for Montague, P.E.I., where he will take over the practice of his father, Dr. T. V. Grant.

The Colchester County Hospital, Truro, estimated its operating costs for 1939 at \$3.14 per hospital day.

Dr. W. Douglas Piercey (Dal., '34) who has been at the Bristol Eye Hospital, Bristol, England, has accepted the position of assistant superintendent at the Ottawa Civic Hospital.

Investigation has shown that Halifax Board of Health regulations, requiring medical certificates every six months of all persons handling foodstuffs, are not enforceable, either legally or practically.

A Red Cross Outpost hospital has been opened at Guysborough, to serve emergency cases in this sparsely populated part of the province. A large house has been acquired on a beautiful site overlooking the harbour, and has been equipped by the Red Cross Society.

The Sutherland Memorial Hospital, Pictou, again showed a small operating profit for the year 1939.

The health division of the Council of Social Service Agencies, Halifax, had begun an investigation of existing legislation designed to control the spread of venereal disease. Large concentrations of troops in this area make the problem even more serious than normally.

ARTHUR L. MURPHY

Ontario

The annual report of the President of the University of Western Ontario lists a total of 2,382 students registered. Of these 197 men and 15 women registered in medicine.

The reduction in Provincial grants to Western, Toronto, and Queen's Universities made an increase in fees imperative in these three Universities. The increase is approximately \$25.00 in each of the years of medical study.

The Hippocratic Society of the University of Western Ontario held its fortieth annual banquet on December 7th, with Dr. R. R. Graham, of Toronto, the invited guest. He spoke on "The evolution of gastric and duodenal surgery".

Dr. J. A. Dobbie has been appointed Superintendent of the Ottawa Civic Hospital to succeed Dr. D. M. Robertson who has retired after long and devoted service. Dr. Dobbie had been an efficient associate of Dr. Robertson for some time past. Dr. W. Douglas Piercey has been appointed Assistant Superintendent. He has been on duty at the Bristol Eye Hospital, Bristol, England.

The issue of the *Hamilton Spectator* for December 16th last contained a health section of eight pages. It is a notable record of the various health activities of the Ambitious City, beginning with its Civic Health Department and an excellent picture of the new health headquarters. Much information is given in detail regarding the maternal death rate, the work of the Mental Health Clinic, school health work, nurses in public health, the Mountain Sanatorium, and its clinic within the city, the Victorian Order of Nurses, food inspection, and the work of the Health Department's dental division. The hospitals received notice.

The class of 1910, University of Toronto, Faculty of Medicine, will hold its first reunion to commemorate the thirtieth anniversary of graduation during the combined meeting of the Canadian Medical Association and the Ontario Medical Association in Toronto, June, 1940. An active local committee is preparing for a large attendance. Every member of the class has been written to and is urged to make his plans to be present.

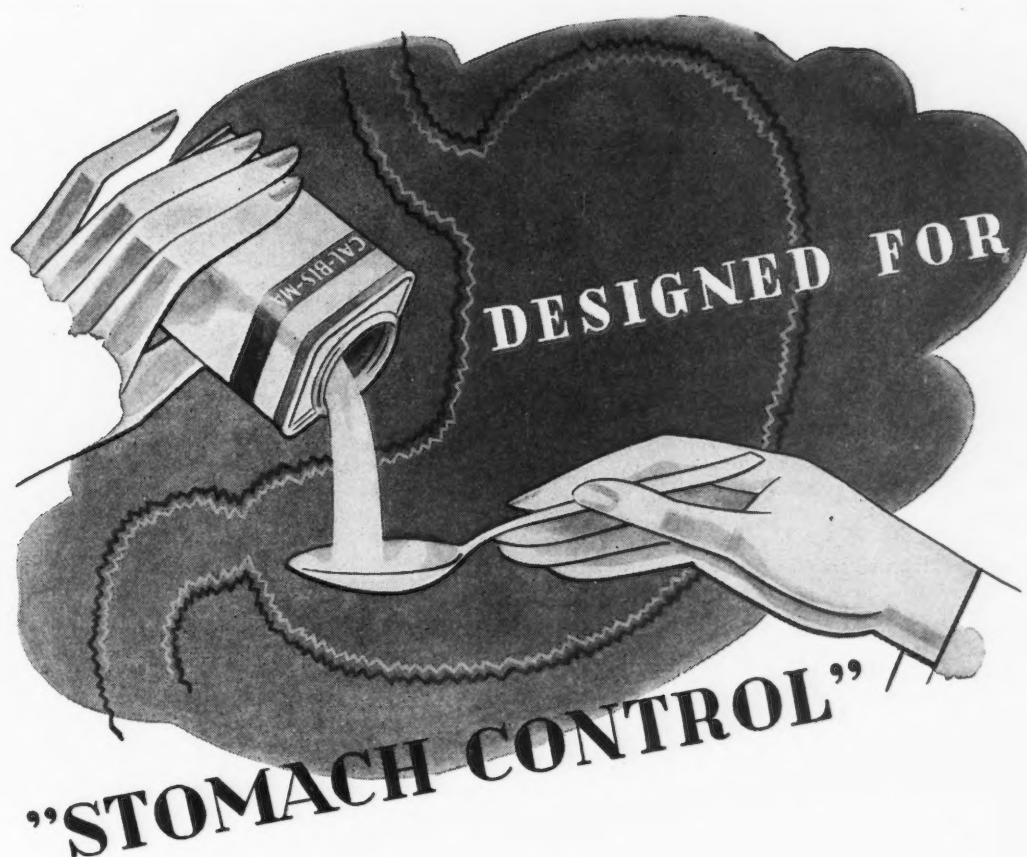
J. H. ELLIOTT

General

Two noteworthy improvements in Eastman x-ray intensifying screens—a unique method of mechanical mounting, and a new type of waterproof coating for both front and back surfaces—are announced by the Kodak Company.

These new fixtures are intended to eliminate annoyances commonly encountered in the mounting and use of screens—such as buckling of the screens, improper contact, chemical deterioration as a result of using certain adhesives, and difficulty of removing screens without injury to them or to the cassette lining.

All three types of Eastman intensifying screens are now prepared, during manufacture, for mechanical mounting, and any cassette can be readily adapted to accommodate them. The back screen is fastened to the cassette cover with four small bolts of special design, furnished with the screens, and the front



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screen is placed loosely in the cassette, or lightly tipped in place. At need, screens may be removed and re-installed without damage.

The new-type waterproofing coating on both the front and back of Eastman intensifying screens serves several purposes. First, it completely protects the active surface against abrasions and wear. In addition, it prevents absorption of moisture, either from humid air, or during washing of the screen. Thus, buckling of the screens is precluded, so that even contact is maintained at all times over the entire screen area.

Both mechanical mounting and the new protective coating are exclusive with Eastman intensifying screens, and they are available at no increase in price.

Book Reviews

Pneumonia, with Special Reference to Pneumococcus Lobar Pneumonia. R. Heffron. 1886 pp. \$4.50. Commonwealth Fund, New York, 1939.

This book is an outcome of the Massachusetts Pneumonia Study conducted by the State Department of Public Health for the five years of 1931-35. Dr. Heffron has produced a most comprehensive review of pneumococcus lobar pneumonia. On the clinical side the volume deals with the lesions produced, diagnosis, factors influencing recovery, and methods of treatment including discussions of medical care, anti-serum, oxygen, vaccine and chemotherapy. Other chapters are devoted to a discussion of the inciting agent, methods of its transmission, and the complex subjects of immunity and prevention of the disease.

In spite of the author's statement that the bibliography is incomplete, no less than 1,471 references have been consulted. It would be a difficult task indeed to name a problem related to this subject which is not fully covered in this excellent book. It is unquestionably the most complete reference work on pneumococcal pneumonia yet published.

Treatment of Some Common Diseases. Edited by T. R. Hill. 398 pp., illust. \$4.50. Macmillan, Toronto, 1939.

In this book some twenty-five medical and surgical subjects of interest to general practitioners are discussed by a score of writers.

The main value of this book seems to lie in many chapters of a special character, sometimes rather cursorily dealt with in the average textbook. Delay in Labour, by A. W. Bourne, presents the causes of prolonged labour in a concise manner, while conservative methods of dealing with this condition are outlined clearly. The subject of Uterine Hæmorrhage has been covered adequately, though Hypothyroidism has not been stressed nor are the newer methods of administering heat to the pelvic organs explained.

Under Head Injury and its Complications the general management of acute injuries is well discussed and thoroughly up-to-date methods are advocated throughout, with due importance attached to dehydration treatment and the use of lumbar puncture. One cannot agree, however, that all early cases of depressed fracture of the skull should be treated conservatively, as immediate elevation with good technique is almost without risk, and offers an early opportunity of dealing with underlying damage. One might further disagree with the statement that closed, depressed fractures should be treated conservatively until they cause symptoms.

Infections of the Face and Neck are discussed in a practical and comprehensive way.

There is a useful chapter on X-ray in the Treatment of Malignant Disease and Injuries to the Skin and Mucous Membranes. The article on Dental Caries

is a concise statement of the more recent trend of thought in this field.

Textbook of Occupational Diseases of the Skin. L. Schwartz and L. Tulipan. 799 pp., illust. \$10.00. Lea & Febiger, Phila., 1939.

This comprehensive monograph is a timely and exceedingly valuable contribution to medical literature.

An attempt has been made here to describe the pertinent industrial processes and the chemicals employed. Particular stress is laid on industry in the United States. The subject matter has been arranged according to trade, occupation and profession, as well as according to the agents producing the dermatoses. The listing of trades and the common noxæ pertaining to each is particularly valuable, and simplifies the problem of determining the causative agents in a particular case. The authors wisely stress the importance of patch testing. The study of industrial dermatoses has been tremendously advanced since the discovery and elaboration of this method. Patch testing, however, has its limitations, false positives and false negatives being all too common. Clinical testing, where practical, is still the best method.

The authors deal briefly with the compensation laws in various countries. They stress the tremendous variability in the laws in various countries and in the different sections of the same country. There is need for a complete overhauling and standardization of the laws of compensation, in this country in particular.

This is a timely book. It is a mine of information and should be in the library of anyone interested in industrial medicine as well as in that of the dermatologist.

Principles and Practice of Aviation Medicine. H. G. Armstrong. 496 pp. \$6.50. William Wood, Baltimore, 1939.

It is not often that a textbook brings together as much new information as does this one—new, that is, to medical readers. As the author says, there are thousands of references in the literature but they are difficult to obtain and are not generally known. Bauer's book appeared in 1926. At that time airplane speeds of 240 miles per hour were spoken of with awe, and the effects of high altitudes, while recognized, had not been worked out in any detail. Now, speeds have increased sharply, together with the rate of rising, which introduces other complications.

Dr. Armstrong's book is extremely interesting, and this is high praise indeed in these days and in respect to a textbook. Mechanical details are brought in just enough to emphasize their physical and medical applications. The chapters on effects of decreased atmospheric pressures and aero-embolism are particularly striking, with the illustrations of the appearance of water vapour and nitrogen bubbles in the blood. The author also includes his own observations on the mental and physical reactions which occur when falling through space, as in parachute jumping. These should be reassuring to everyone who feels he may ever have to face the experience. It is interesting to note that very little work has been done on the effects of flying on passengers with such diseases as arteriosclerosis, cardiac weakness, anæmia, etc.

More care might have been taken in the proof reading. But that is the only criticism of a book which is well worth having.

Pioneers in Acute Abdominal Surgery. Z. Cope. 134 pp. \$2.25. McAllister, Toronto, 1939.

Mr. Zachary Cope is well equipped, both in a professional and literary sense, to write the story of the pioneers in acute abdominal surgery, and the tale he tells is a fascinating one. His purpose is chiefly to pay honour to pioneers in this field, some of whom were surgeons stationed far from the large centres of academic learning. Many of the names Mr. Cope mentions are familiar: Celsus, Petit, Dupuytren, Lister,

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MANUFACTURING CHEMISTS TO THE MEDICAL PROFESSION SINCE 1858

Spencer Wells, Lawson Tait, John Hilton, and Jonathan Hutchinson, Mikulicz, R. H. Fitz, and Charles McBurney, but it is pleasing to read of the patient efforts of many others almost unknown to fame, such as Benjamin T. Travers, Dieffenbach, Frank T. Paul, George Freer, Amussat, Lindstedt, Henry Clark, Henry Hancock, Willard Parker, and Hallwright, who had the vision and courage to be the first to undertake or to suggest operative measures which have saved countless human lives. It is refreshing in these days when war brings wholesale destruction to read of these triumphs of peace through the efforts of surgeons of many lands and of differing races.

Office Gynecology. J. P. Greenhill. 304 pp., illust. \$3.00. Year Book Publishers, Chicago, 1939.

This book fills a long felt want. It tells both the tyro and the experienced how best to carry out the various diagnostic and treatment techniques in gynecology which may be undertaken in the doctor's office or as out-patient hospital procedures. Some of these, of course, are strictly specialist procedures, but there are a great number which the general practitioner will find of value.

The chapters are short and concise but the descriptions of such common and important undertakings as cauterization of the cervix, insertion of pessaries, vaginal douches, etc., are very well done and the text is not loaded with a large number of alternative techniques. There is an excellent chapter on post-partum care, in which the value of bed exercises is stressed. There is another excellent, if too short, description of that most common female complaint, backache. The account of birth control is one of the best we have seen, and includes a description of the "safe" period.

While it is doubtful if such chapters as those on pneumoperitoneum and sterilization by coagulation of the uterine cornu do not constitute works of supererogation, and should be dropped from subsequent editions because of their dubious value even to a specialist, they do not spoil a book that every general practitioner who wishes to keep abreast of gynecological diagnostic and minor therapeutic technique, should have on his shelves.

Cæsarean Section: Lower Segment Operation. C. M. Marshall. 230 pp., illust. \$6.25. Macmillan, Toronto, 1939.

The book is founded on an extensive reading of the literature and a personal experience of 250 operations. It deals with the *operative* aspect of intraperitoneal lower segment Cæsarean section, a procedure which, in the author's opinion, presents the only truly strategic and really surgical approach to the cavity of the pregnant uterus. The author makes out a strong case for the transverse as opposed to the longitudinal incision in the lower segment. Goertler's researches into the essential structure of the uterine wall seem to substantiate this view. There is an interesting chapter on anaesthesia; spinal anaesthesia and, in particular, local anaesthesia are favoured, though the dangers of spinal anaesthesia are not minimized.

Details are given of the 250 operations, which include a suspect or infected group of 71 cases; placenta prævia, 44; albuminuria, pre-eclampsia or eclampsia, 19; heart disease, 14; and cases of favourable omen, 102. There was not a single maternal fatality, though it is admitted that there were at least nine who must narrowly have escaped death.

A word of praise must be given to the publishers for a book which is a delight to the eye. The coloured plates are things of beauty. This work is a notable contribution to obstetric literature.

Brucellosis in Man and Animals. I. F. Huddleson *et al.* 339 pp., illust. \$3.50. Commonwealth Fund, New York, 1939.

Brucellosis in man and animals is a major public health problem in America. According to Hardy its

past or present prevalence in man cannot be determined reliably. The reported cases of human brucellosis rose steadily in the United States from 24 in 1925 to 2,497 in 1936. Hardy thinks, however, that the true incidence has decreased during this period. The increase in reported cases doubtlessly results from more accurate methods of diagnosis, for which the chief author of this book deserves a very considerable share of the credit. In 1934 he published "Brucella Infections in Man and Animals", which dealt with methods of laboratory diagnosis. The book under review is a new edition of this previous work and an extension of it to cover, in short compass, all aspects of the disease.

Brucellosis in man and animals is considered from clinical and laboratory standpoints. There are excellent sections on its bacteriology and epidemiology. Giltner discusses fully the methods and results of attempts at the control and eradication of the sources of brucellosis infection.

The book satisfies the need for a comprehensive monograph on this increasingly important disease and will be valued by all who are interested in it, whether from the clinical, laboratory or public health aspects.

Urine Examination and Clinical Interpretation. C. E. Dukes. 403 pp., illust. \$7.50. McAinsh, Toronto, 1939.

This book by the pathologist to St. Peter's Hospital (for Stone and other Diseases of the Urinary Organs) and to St. Mark's Hospital, London, is based on the rich experience which the holder of these positions must have in the examination of urine and in the interpretation of the results of such examinations. The purpose of the author has been to help "general practitioners, physicians and surgeons" to understand the clinical significance of the various findings and their precise uses and limitations.

The work is sound and authoritative, with nothing essentially new in the ordinary methods of examination. Considerable space, however, is given to biological methods of assaying hormone content of urine with several excellent coloured plates, and some consideration is also given to the determination of deficiency of vitamins C and B.

The section on renal function tests is very practical, with full details of the most commonly employed methods. The discussion of the urea-clearance test is unusually lucid. In discussing renal tuberculosis the statement is made that "symptoms do not manifest themselves until extensive lesions have developed in the kidney". The experienced urologist sees many cases of renal tuberculosis in which the lesions are very minute and yet symptoms are typical. This, however, is a minor point and the book can be recommended as a useful and readable work for the laboratory worker and clinician.

The Physiological Basis of Medical Practice. C. H. Best and N. B. Taylor. 2nd edition, 1872 pp., illust. \$10.00. Williams & Wilkins, Baltimore, 1939.

Two years after its first appearance the authors are bringing out the second edition of this extraordinary book. To students and practitioners and particularly to those working for post-graduate degrees this event will be hailed with delight, signifying as it does the authors' intention to maintain the work abreast of the rapidly moving facts and theories of applied physiology.

The principal addition has been a 200 page section on the special senses but, as well, notable changes have been made in the vitamins, the endocrines and heparin, and there are scattered throughout the text numerous alterations and additions, bringing the whole up to date.

To be critical one might, perhaps, find the section on the physics of sight and sound rather too detailed for the average reader but this does not detract from

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the book as a whole, and in this reviewer's opinion it is still the ablest and the most readable text obtainable on clinical physiology.

Public Health Law. J. A. Tobey. 2nd ed., 414 pp. \$3.50. Commonwealth Fund, New York, 1939.

Dr. Tobey's book presents a difficult problem for a Canadian reviewer. For the Canadian reader whose acquaintance with the law, and especially the constitutional law, of the United States is casual and fragmentary, those portions of the monograph which consist of an exposition of legal principles may prove misleading. The law of Canada differs in many essential respects from that which applies in the United States, especially in those instances where the conduct of the citizen is governed by statute, and it is impossible, in the space which can be devoted to a review, to draw attention to points of similarity and points of difference with sufficient amplitude to guard the Canadian reader against misapprehension.

Yet there is much in this monograph which is of the utmost importance to those interested in the legal side of public health, much that is not strict law but rather sound advice offered by an experienced administrator and student of public health administration to other administrators as to the course which they should adopt in putting public health laws into effect. We should be sorry, indeed if this review were to lead Canadian health officials to ignore this excellent volume. If the reader bears in mind the hazards we have indicated he should profit from a perusal of Dr. Tobey's study.

Stedman's Medical Dictionary. T. L. Stedman and S. T. Garber. 14th ed., 1303 pp., illust. \$7.00, with index \$7.50. Williams & Wilkins, Baltimore, 1939.

Although the senior author has passed, the dictionary has been continued with the same excellence. Many of the newer words are included. The same emphasis has been placed on the derivation of words. The correct pronunciation is given. The anatomical nomenclature is that of the B.N.A., but an appendix has been added giving the Birmingham Revision with its B.N.A. equivalent. A good medical dictionary is an essential today. This one has held a valued place on the bookshelves of physicians for many years, and now that its continuance is assured will hold at least an equal place with its predecessors.

Topographic Atlas for X-ray Therapy. I. I. Kaplan and S. Rubinfeld. 120 pp. \$4.00. Year Book Publishers, Chicago, 1939.

A useful work for those engaged in x-ray practice.

Annual Review of Physiology, Vol. 1. J. M. Luck, Editor. 705 pp. \$5.00. American Physiological Society and Annual Reviews, Inc., Stanford University P.O., California, 1939.

As stated in the preface, the editorial committee attempts to place before the reader in one volume a comprehensive survey of the year's research in physiology. The book comprises 24 chapters, each covering a separate division of the field, and in all some 34 reviewers have collaborated. There is a careful index and an extensive bibliography follows each chapter. A noteworthy effort, the book will be of greatest usefulness to workers in physiology and the associated sciences. Much of the work reported is not yet ready for the clinician's assimilation, but those who wish to keep entirely abreast will find it a ready, if rather indigestible, source of information.

Medical Climatology. C. A. Mills. 296 pp. \$4.50. C. C. Thomas, Springfield, 1939.

This is an intensely interesting monograph dealing with medicine in a wider dimension. The author has summarized the essential material and conclusions in the great mass of literature dealing with the effects of climatic environment on health and disease, and has arranged the data so that their implications in the

practice of medicine are apparent. The presentation gains in interest and force as the greater part of the illustrative material is drawn from the work of the author and his Cincinnati associates in this field.

The result is a book which will make exciting reading for any physician. The basic thesis is the statement that the ease or difficulty of body heat loss plays a dominant rôle in the existence of man. The effect of weather on this oxidation level is considered from many aspects. While one may question some of the conclusions (it is difficult to consider climatic influences apart from other coincident factors), there is no doubt that there is now a most impressive amount of evidence to show that weather conditions and seasonal and regional factors have a marked influence on life and disease on this continent. As the author says, "No longer can the profession and medical scientists safely ignore these intrinsic factors that basically influence the fundamentals of human existence."

Practising physicians will be most interested in the evidence here set down—some of it startling—dealing with the effect of climate on such diseases as diabetes, goitre, pernicious anaemia, acute appendicitis, leprosy and acute rheumatic fever. There is a valuable chapter concerning the most favourable region of the country for various diseases in those cases where a change of climate is sought. Beyond these specific matters there are stimulating commentaries on such questions as the significance of the rise in sickness and death noted in winter months in this country, the incidence of mental breakdown, the influence of climate on growth, the development and fertility, the problem of the degenerative diseases, the medical possibilities of air-conditioning, the relation between climate and the rapid tempo of life on this continent. Two other questions of the greatest interest are a study of the climatic drive in various parts of the world with tables setting out the index of climatic stimulation, and a summary of climatic changes in geological and recorded history.

This book has the merits of clarity and imagination. It records what frequently happens when medical questions are considered within the wider frame of reference of biology.

Nutrition and Physical Degeneration. W. A. Price. 431 pp., illust. \$5.00. P. B. Hoeber, New York, 1939.

When the eyes of the medical world are directed towards nutrition in all its phases, and our medical journals are devoting much space to the discussion of the practical side of the question, it is a most opportune time to consider a masterpiece of research into the question from the dental viewpoint. Dr. Price has long been known for his experimental work in preventive dentistry, and most of his conclusions have been accepted by the dental profession. And now for his crowning contribution, he has visited five continents and sailed the southern seas to gather facts from primitive peoples who have escaped the deadly touch of civilization and to compare them with other members of the tribe who have been living close to the white man and have changed the tribal food for flour and sugar. He gathers his facts together in a book which is beautifully illustrated with original and convincing photographs, and has produced a work that is most readable, for, stepping aside from the logic of arithmetic, he finds time to record some of his personal experiences in these remote districts, seldom visited by white man.

In spite of all the experimental work that has been done on nutrition, the majority of the medical profession are frankly unconvinced by results obtained from guinea pigs and rabbits. Dr. Price has overcome their objections by bringing the laboratory and the human patient together, and there can be no escape from his conclusions. As far as mathematics is concerned, he has done for nutrition what Pawlow did for digestion.